DESIGN AND EVALUATION OF GASTRORETENTIVE TABLETS OF LEVETIRACETAM

Dissertation submitted to

The Tamilnadu Dr. M.G.R Medical University, Chennai -32

In partial fulfillment of the requirements
For the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

By

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Under the guidance of

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KRISHNANKOIL-626 126, VIRUDHUNAGAR DISTRICT, TAMILNADU

APRIL- 2013

CERTIFICATE

This is to certify that the investigation described on this thesis entitled **"DESIGN AND EVALUATION OF GASTRORETENTIVETABLETS OF LEVETIRCETAM"** is submitted by **Reg.No.26113903 of Arulmigu Kalasalingam College of Pharmacy**, **Anand Nagar, Krishnankoil-626126, Virudhunagar- District, Tamilnadu** affiliated to **the Tamilnadu Dr. M.G.R. Medical University, Chennai** for the partial fulfillment of degree of Master of Pharmacy in Pharmaceutics under the guidance and supervision of **Mr.V.Sivakumar ., M.Pharm.,**

I wish him all the best in his future endeavors.

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EVALUATION CERTIFICATE

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1.

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I take this opportunity to express my love and deep sense of gratitude to my family who have been a great moral support all through my life, and my success at every stage of life is because of their unconditional love for me and staunch belief in my abilities.

Dedicated

to

My Beloved parents

and

Friends

List of Abbreviations

FDDS	-	Floating drug delivery system
HCl	-	Hydrochloric acid
HPMC	-	Hydroxypropylmethylcellulose
PEO	-	Polyethylene Oxide
MCC	-	Microcrystalline cellulose
IPA	-	Isopropyl alcohol
PVP	-	Polyvinyl pyrollidone
B.P	-	British Pharmacopoeia
I.P	-	Indian Pharmacopoeia
DSC	-	Differential Scanning Colorimeter
FTIR	-	Fourier Transform Infrared spectroscopy
U.V	-	Ultra Violet spectroscopy
HPLC	-	High Performance Liquid Chromatography
AUC	-	Area under the curve
AUMC	-	Area under the first moment curve
Cmax	-	Peak plasma concentration
tmax	-	Time of peak concentration
GIT	-	Gastro intestinal tract
GI	-	Gastro intestinal
Fig	-	Figure
q.s	-	quantity sufficient
RSD	-	Relative standard deviation
SD	-	Standard deviation
RH	-	Relative Humidity
ICH	-	International Conference on Harmonization

Nomenclature

rpm	-	Revolutions per minute
mm	-	millimeter
gm	-	gram
mg	-	milligram
ml	-	milliliter
cm	-	centimeter
mcg/hr	-	microgram per hour
ng/hr	-	nanogram per hour
mg/h	-	milligram per hour
w/w	-	weight/weight
%	-	Percentage
hr	-	Hour
sec	-	Seconds
mins	-	Minutes
kg/cm^2	-	kilogram per square centimeter
gm/ml	-	Gram per milliliter

1. INTRODUCTION

1.1. Introduction to Floating Drug Delivery Systems

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process [1].

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.

These immediate release dosage forms have some limitations such as [2, 3]:

1) Drugs with short half-life require frequent administration, which increase the chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes it difficult to attain steady state condition.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the C_{ss} values fall or rise beyond the therapeutic range.

4) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug

delivery system that could revolutionize method of medication and provide a number of therapeutic benefits [4].

1.2. Introduction to Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue [5].

Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release
2) Sustained release
3) Site-specific targeting
4) Receptor targeting

More precisely, Controlled delivery can be defined as [6]: -

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2) Localized drug action by spatial placement of a controlled release system adjacent to (or) in the diseased tissue.
3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug.

1.2.1. Advantages of Controlled Drug Delivery System

1. Avoid patient compliance problems.
2. Dosage frequency were reduced
3. Improve efficiency in treatment
4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

1.2.2. Disadvantages of Controlled Drug Delivery System

1) Decreased systemic availability in comparison to conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro – in vivo correlation.
3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
4) Retrievals of drug are difficult in case of toxicity, poisoning or hypersensitivity reactions.
5) Reduced potential for dosage adjustment of drugs normally administered in varying strengths.

1.3. Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage form (solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology. Therefore the scientific framework required for the successful development of oral drug delivery systems consists of basic understanding of (i) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug (ii) the anatomic and physiologic characteristics of the gastrointestinal tract and (iii) physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

The main areas of potential challenge in the development of oral controlled drug delivery systems are: -

- Development of a drug delivery system: To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
- Modulation of gastrointestinal transit time: To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for a prolonged period of time to maximize the delivery of a drug dose.

- Minimization of hepatic first pass elimination: If the drug to be delivered is subjected to extensive hepatic first-pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

Conventional oral controlled dosage forms suffer from mainly two adversities [13]. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms.

Altering the gastric emptying can overwhelm these problems. Therefore it is desirable, to formulate a controlled release dosage form that gives an extended GI residence time. Extended release dosage form with prolonged residence time in stomach are highly desirable for drugs.

i. That are locally active in stomach,
ii. That have an absorption window in the stomach or in the upper small intestine,
iii. That are unstable in the intestinal or colonic environment,
iv. Have low solubility at high pH values.

1.4. Gastro retentive Dosage Form (GRDF)

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

1.4.1. Biological Aspects of GRDFs [7, 8, 9, 10, 11]

Role of GI tract:

Stomach

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area, very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

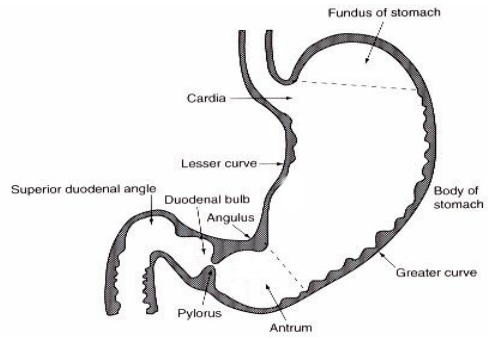


Fig1: Anatomy of Stomach

The stomach is divided into three anatomical regions. i) Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consists of fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. They are digestive mode and inter digestive mode. In case of fasted state an inter digestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as inter digestive my electric cycle.

Phase I	Period of no contraction.
Phase II	Period of intermittent contraction.
Phase III	Period of regular contractions at the maximal frequency that migrate distally.
Phase IV	Period of transition between phase III and phase I.

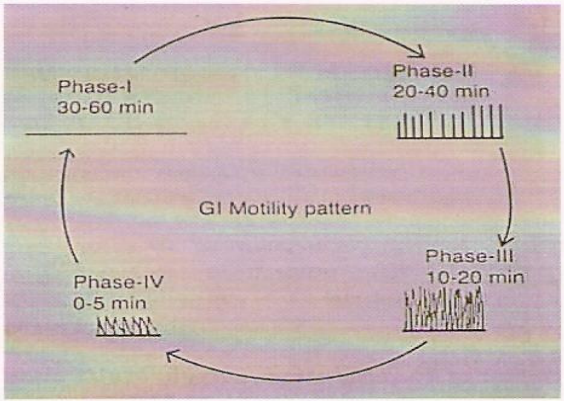


Fig 2: Gastro intestinal motility pattern

PHASE I: The quiescent period, lasts from 30 to 60 mins and is characterized by a lack of secretary, electrical and contractile activity.

PHASE II: Exhibits intermittent activity for 20-40 min, during which the contractile motions increase in frequency and size. Bile enters the duodenum during this phase,

whereas gastric mucus discharge occurs during the latter part of phase II and throughout phase III.

PHASE III: Has a housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

PHASE IV: Is the transition period of 0-5 mins between Phase III & I.

1.4.2. Requirements for Gastro Retention

From the discussion of the physiological factors in stomach, to achieve gastro retention, the dosage form must satisfy some requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and constant grinding and churning mechanisms. It must resist premature gastric emptying and once the purpose has been served, it should be removed from the stomach with ease

1.5. Approaches to Gastric Retention [9, 10, 11, 12]

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Floating systems, Bio adhesive systems, swelling and expanding systems, High density systems, Modified systems

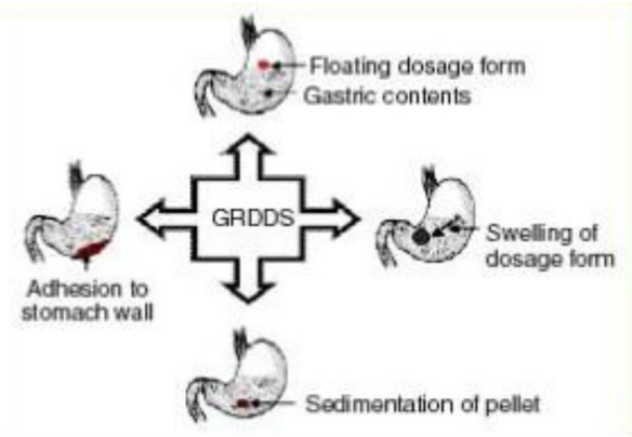


Fig 3: Classification of gastro retentive drug delivery system

1.5.1. Buoyant/ Floating Systems

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

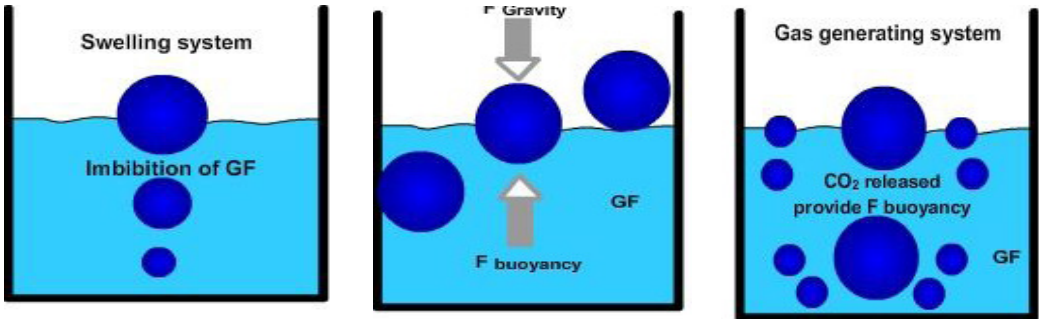


Fig 4: Mechanism of floating system

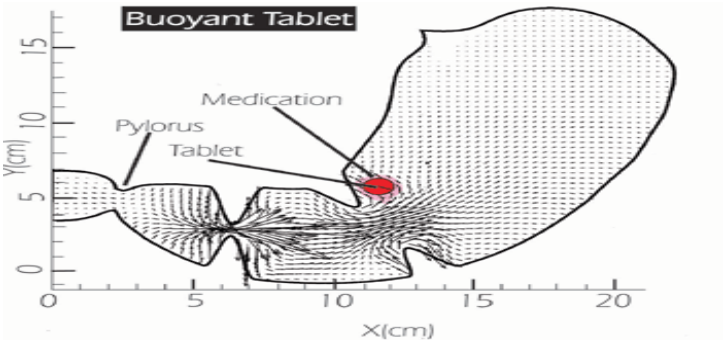


Fig 5: Graphic of Buoyant tablet, which is less dense than the stomach fluid and therefore remains in the fundus.

1.5.2. Bio/Muco-adhesive Systems

Bio/muco-adhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane.

The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on bio/muco-adhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI wall provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect. Binding of polymers to the mucin/epithelial surface can be divided into three broad categories: –

1. Hydration-mediated adhesion.
2. Bonding-mediated adhesion.
3. Receptor-mediated adhesion.

1.5.3. Swelling and Expanding Systems

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "*plug type system*", since they exhibit the tendency to remain logged at the pyloric sphincter if that exceeds a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity. Such polymeric matrices remain in the gastric cavity for several hours even in the fed state.

1.5.4. High Density Systems

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which such systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. They are retained in the antrum of stomach as shown in Fig. 6.

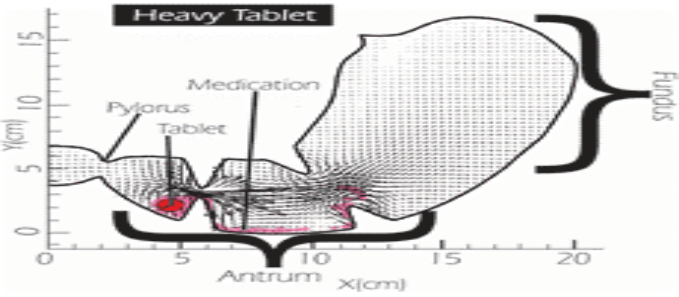


Fig 6: Graphic of heavy tablet, which is denser than the stomach fluid and therefore sinks to the antrum

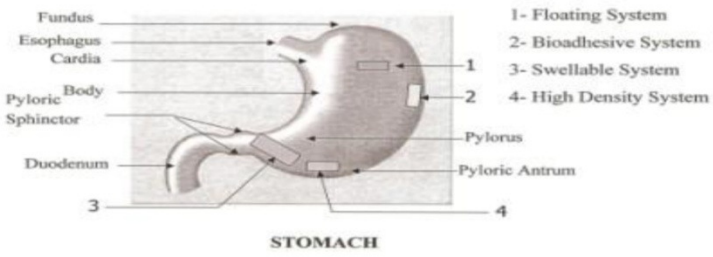


Fig7: Physiology of gastro intestinal tract

1.5.5. Incorporation of Passage Delaying Food Agents

Food excipients like fatty acids e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

1.5.6. Ion Exchange Resins

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

1.5.7. Osmotic Regulated Systems [13]

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio erodible capsule. In the stomach the capsule quickly disintegrates to release the intra gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components – drug reservoir compartment and osmotically active compartment.

1.6. Types of Floating Drug Delivery Systems (FDDS) [14, 15]

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and

B. Non- Effervescent System.

1.6.1 Effervescent System

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

I. Gas Generating systems

II. Volatile Liquid/Vacuum Containing Systems.

1.6.1.1 Gas – Generating Systems

Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS)

These are as shown in Fig.8 and formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

1. **Intra Gastric Single Layer Buoyant Tablet**

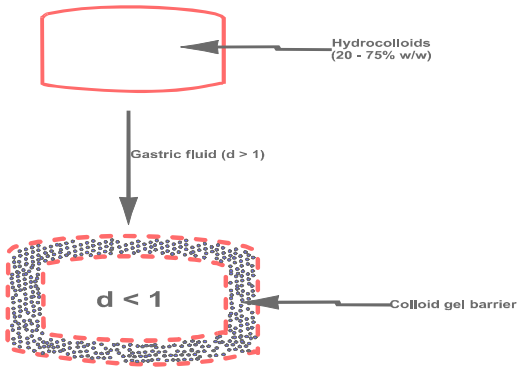
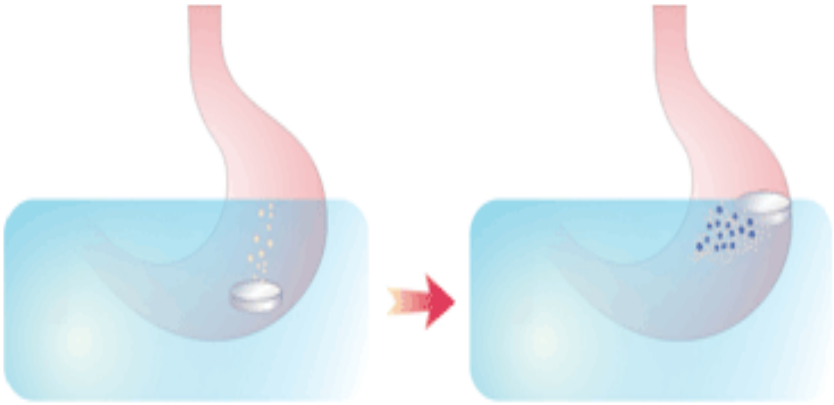


Fig 8: Intra Gastric Single Layer Buoyant Tablet



1.6.1.1.1. Intra Gastric Bilayer Floating Tablets

These are also compressed tablet as shown in Fig 9 and containing two layers i.e.

i. Immediate release layer and

ii. Sustained release layer.

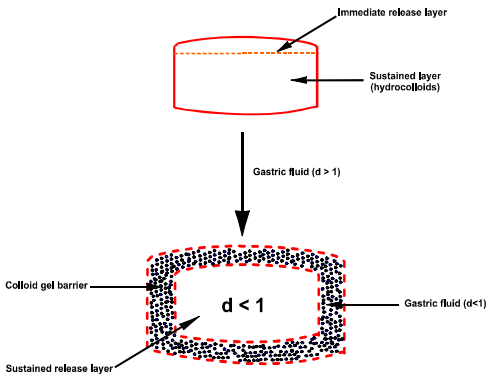


Fig 9: Intra Gastric Bilayer Buoyant Tablet.

1.6.1.1.2. Multiple Unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layers consist of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

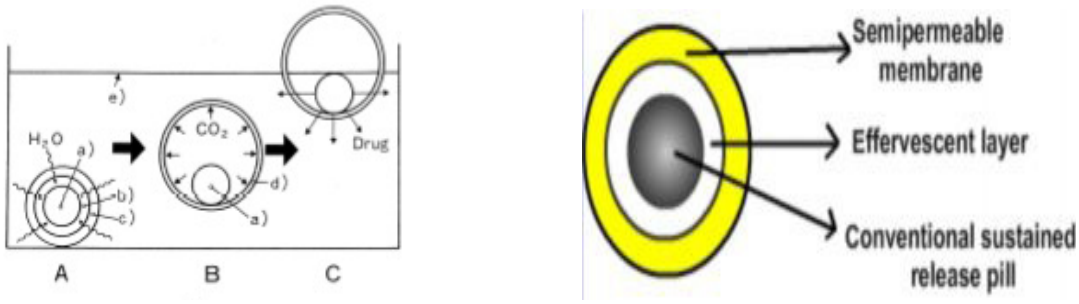


Fig 10: A multi-unit oral buoyant dosage system. Stages of floating mechanism: (A) penetration of water (B) generation of CO_2 and floating (C) dissolution of drug. Key: (a) conventional SR pills (b) effervescent layer (c) swellable layer (d) expanded swellable membrane layer (e) surface of water in the beaker (37^0C)

1.6.1.2. Volatile Liquid / Vacuum Containing Systems [16]

1.6.1.2.1. Intragastric Floating Gastrointestinal Drug Delivery System

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a micro porous compartment, as shown in Fig11.

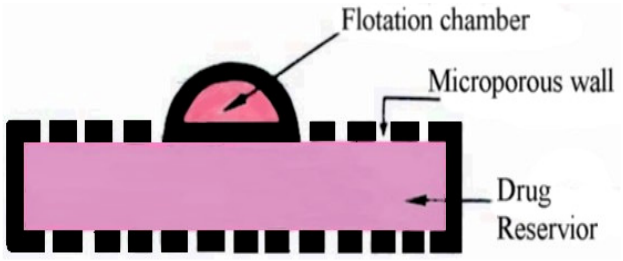


Fig11: Intra Gastric Floating Gastrointestinal Drug Delivery Device

1.6.1.2.2. Inflatable Gastrointestinal Delivery Systems

In these systems, an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir,

which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule.

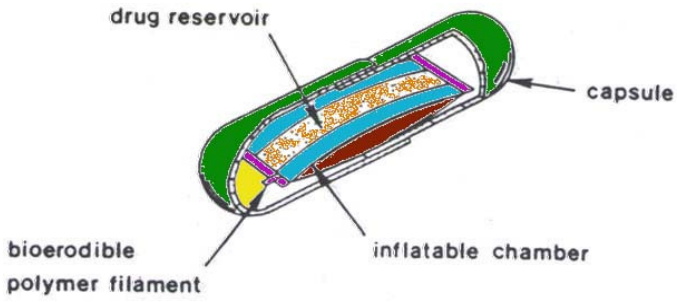


Fig 12: Inflatable Gastrointestinal Delivery System

After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug is continuously released from the reservoir into the gastric fluid. This system is shown in Fig12.

1.6.1.2.3. Intragastric Osmotically Controlled Drug Delivery System

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intra gastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to

dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bio erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig13.

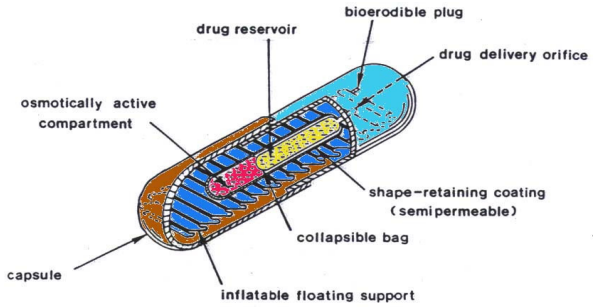


Fig13: Intragastric Osmotically Controlled Drug Delivery System

1.6.2. Non-Effervescent Systems [16]

The Non-effervescent FDDS is based on the mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. The various types of this system are as:

1.6.2.1. Single Layer Floating Tablets

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

1.6.2.2. Bilayer Floating Tablets

A bilayer tablet contains two layers, one immediate release layer which release initial dose from system while the another sustained release layer which absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

1.6.2.3. Alginate Beads

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours.

1.6.2.4. Hollow Microspheres

Hollow microspheres (micro balloons), loaded with drug in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 40^0C.

The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed an internal cavity in microsphere of polymer with drug. The micro balloons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*.

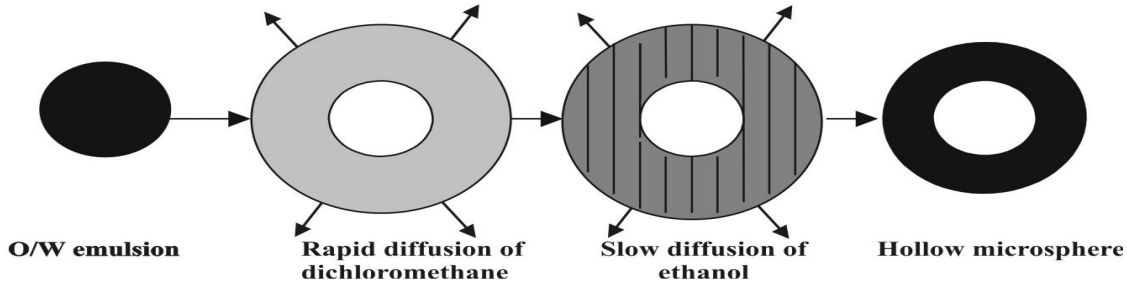


Fig14: Hallow microspheres

1.7. Factors Controlling Gastric Retention Time of Dosage Form

The gastric retention time (GRT) of dosage form is controlled by several factors that affect their efficacy as a gastro retentive system.

- **Density of dosage form**: –density of gastric fluid is reported to be 1.004g/cm^3, density of the dosage form should be less than this for buoyancy, so that it is retained in stomach for longer period of time. The dosage form may be having a high density in the beginning, but due to reduction in density by swelling it will float in stomach.
- **Size of the dosage from**: –studies on the effect of particle size on gastric retention have been inconclusive. In general it is known that indigestive solids larger than 1-2mm are retained in stomach throughout the post-prandial period, after which they are emptied in stomach throughout the post-prandial period, after which they are emptied by cyclically recurring burst of inter digestive gastric contractions. However studies have suggested that this observation cannot be generalized. Many recent studies have shown that non-disintegrating tablets as large as 7mm can be emptied from human stomach during the post-prandial period, while 13mm tablets are retained until arrival of subsequent sweeping “housekeeper wave”. This emphasizes the need for size enlargement of DF in stomach in order to prolong GRT.

- **Shape of dosage form** – Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KPSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.
- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.
- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.
- **Caloric content** – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.40.6 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.

1.8 Advantages of FDDS [17, 18]

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patient compliance.
8. Site-specific drug delivery.

1.9 Disadvantages of FDDS

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.
4. Gastric emptying of floating forms in supine subjects may occur at random and becomes highly dependent on the diametral size. Therefore patients should not be dosed with floating forms just before going to bed.

Table1: 1. 14 Lists of Drugs - Floatable Drug Delivery Systems

S. No.	DOSAGE FORM	DRUGS
1	Microspheres	Aspirin, Grisiofulvin, p-nitroanilline, Ibuprofen, Terfinadine, Tranilast.
2	Granules	Diclofenac sodium, Indomethacin, Prednisolone
3	Films	Cinnarizine
4	Powders	Several basic drugs
5	Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa, benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid
6	Tablets/pills	Acetaminophen, Acetylsalicylic acid, Amoxicillin trihydrate, Ampicillin, Atenolol, Cinnazirine, Diltiazem, Fluorouracil, Isosorbide mononitrate, Isosorbide dinitrate, Piretanide, Prednisolone, Quinidine gluconate, Riboflavin-5-phosphate, Sotalol, Theophylline, Verapamil HCl

Table 2: 1.15 Marketed Products of FDDS

SR. NO.	BRAND NAME	DRUG (DOSE)	COMPANY, COUNTRY	REMARKS

1.	Modular®	Levodopa (100 mg), Benserazide (25 mg)	RocheProducts, USA	FloatingCR capsule
2.	Val release®	Diazepam (15 mg)	Hoffmann-Larches, USA	Floating capsule
3.	Liquid Gavison®	Al hydroxide (95 mg), Mg carbonate (358 mg)	GlaxoSmith Kline, India	Effervescent floating liquid alginate preparation
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidalgel forming FDDS
6.	Cifran OD®	Ciprofloxacin(1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec®	Misoprostal (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule

Miteshkumar J.Patel et al[19]., The aim of this study was to develop a new intra-gastric floating in situ gelling system for controlled delivery of levetiracetam for the treatment of partial onset seizures. High dose of levetiracetam (750 to 1000 mg) is difficult to incorporate in floating tablets but can easily be given in liquid dosage form released. Sodium alginate-based in-situ gelling systems were prepared by dissolving various concentrations of sodium alginate in deionized water, to which drug and calcium carbonate were added. Fourier transform infrared spectroscopy (FTIR) was used to check the presence of any interaction between the drug and the excipients. A 32 full factorial design was used for optimization. The concentrations of sodium alginate (X1) and calcium carbonate (X2) were selected as the independent variables. The amount of the drug released after 1 h (Q1) and 6 h (Q6) and 12 h (Q12) and the viscosity of the solution were selected as the dependent variables. The gels were studied for their viscosity, in-vitro buoyancy and drug release. Other ingredient like HPMC K100M used for strength forming polymer, sodium citrate is used for liquefying solution.

Siahi et al[20]., designed and evaluated 1- and 3- layer matrices of verapamil hydrochloride for sustaining its release, the kinetic analysis of drug release from matrices exhibiting sustained release indicated that release was predominantly attributable to the contribution made by Fickian diffusion.

Krojel et al[21]., developed and evaluated floating and pulsatile drug delivery systems based on a reservoir system consisting of a drug-containing effervescent core and a polymeric coating. For the floating system, a polymer coating with a high elongationvalue and high water- and low CO_2 permeabilities was selected (Eudragit® RL/acetyltributyl citrate 20%, w/w) in order to initiate the effervescent reaction and

the floating process rapidly, while for the pulsatile DDS, a weak, semipermeable film, which ruptured after a certain lag time was best (ethyl cellulose/dibutyl sebacate 20%, w/w).

S. Sungthongjeeh et al[22]., developed a multiple-unit floating drug delivery system based on gas formation technique was developed in order to prolong the gastric residence time and to increase the overall bioavailability of the dosage form. The system consists of the drug-containing core pellets prepared by extrusion–spheronization processes. The time to float decreased as amount of the effervescent agent increased and coating level of gas-entrapped polymeric membrane decreased. The optimum system could float completely within 3 min and maintained the buoyancy over a period of 24 h.

Brijesh s dev et al[23]., prepared a gastroretentive drug delivery system of ranitidine hydrochloride. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. The results of the full factorial design indicated that a low amount of citric acid and a high amount of stearic acid favors sustained release of ranitidine hydrochloride from a gastroretentive formulation.

Sunil k jain et al[24]., developed and evaluated of carrier based orlistat microspheres for gastric delivery consisting of eutragit s as polymer, by solvent evaporation method and to evaluate their gastro retentive and controlled release profile. The effect of various formulation and process variables on the particle morphology.

Patel D M et al[25]., developed gastroretentive drug delivery system of carbamazepine formulation using simplex lattice design. This approach used to achieve increased gastric residence time for the dosage form and sustain drug release.

Gambhir M N et al[26]., developed and invitro evaluation of an oral floating matrix tablets formulation of diltiazem hydrochloride to prolong gastrointestinal residence time and increase it bioavailability. The tablets were prepared by direct compression method, using polymers such as hydroxyl methyl propyl cellulose compritol. Alone or in combination. Sodium carbonate was incorporated a gas generating agent.

Baumgartner et al[27]., developed a optimization of floating matrix tablets and evaluation of their gastric residence time. In vivo experiments with fasted state beagle dogs revealed prolonged gastric residence time. On radiographic images made after 30 minutes of administration, the tablet was observed in animal's stomach and the next image taken at 1 hour showed that the tablet had altered its position and turned around.

R D kale et al[28]., developed a multiple unit floating drug delivery system of piroxicam was prepared using enteric polymer and emulsification solvent evaporation method. The microspheres remained buoyant continuously over surface of the acidic media containing surfactant for a period of 8-12 h in vivo.

Fraces et al[29]., designed a floating dosage forms to proling a gastro retention of the calcium alginate beads. It is a type of multi unit floating gel beads synthesized with calcium alginate, sunflower oil, by gelation process. The alginate beads were able to continuously float over the medium for 24 h. under constant agitation.

Shradda s badve et al[30]., developed hollow/porous calcium pectinate beads for floating pulsatile drug delivery of diclofenac sodium intended for chronopharmacology by process of acid base reaction during ionotropic crosslinking

Mahesh chavanpati et al[31]., studied developed of sustained release gastroretentive drug delivery system of oflaxacin *in-vivo* and *in-vitro* evaluation by using polymers as psyllium husk, hydroxyl propyl methyl cellulose K100M.

Aim

To prepare and evaluate Levetiracetam floating tablets based on gas forming agent.

Objectives of the study

Levetiracetam is a broad-spectrum antiepileptic drug used in the treatment of partial-onset seizures, myoclonic seizures, and generalized tonic-clonic seizures. Levetiracetam though rapidly and completely absorbed in the stomach and the small intestine, is comparatively less bioavailable in the lower part of the intestine. Levetiracetam is used as a monotherapy for seizures. Levetiracetam may be used as an alternative for the syndrome of juvenile absence epilepsy.Treatment of patients with seizures or epilepsy is often challenging. A person suffering from seizures has to strictly adhere to the medications every day. Even missing a dose of the drug may lead to fatality of the patients. The nootropic drug levetiracetam, has a half life of 6-8 hrs, suffers the disadvantage of multiple dosing in a day. To eradicate the disadvantage, the study was designed to reduce the dosage by designing it into a floatable drug delivery which will serve both the purpose of enhancing the absorption in the upper part of the GIT and further sustaining the release of the drug.

PLAN OF WORK

In the present research work, formulation of levetiracetam floating tablets for oral controlled drug delivery system was done with various polymers like HPMC K4M, HPMC E15 and CARBOPOL974 p.

1. Formulation of Levetiracetam floating tablets by wet granulation method, using as hydrophilic polymers HPMC K4M,HPMC E15 and carbopol 974 p and sodium bicarbonate as the gas-generating agent.
2. Twelve formulations were formulated with different proportions of HPMC K4M and HPMC E15M and CARBOPOL 974 P.

The prepared floating tablets will be evaluated for parameter related to controlled drug delivery system like evaluation of granules and evaluation of tablets.

A. Evaluation of Granules:

I) Angle of Repose

II) Bulk density and tapped density

III) Compressibility index

IV) Hausner ratio

B. Evaluation of Tablets

I) Hardness

II) Friability

III) Uniformity of weight

IV) Drug content estimation

V) Buoyancy determination;

a) Buoyancy lag time

b) Duration of Buoyancy

VI) Swelling Index

1. To carry out the in-vitro release studies of levetiracetam from the formulation by using dissolution apparatus.
2. To carry out pre-formulation studies and compatibility studies for possible drug and polymer interactions by using FTIR technique.
3. This prepared floating tablets may fulfill the need of present work.

LEVETIRACETAM

Structure

Molecular formula : $C_8H_{14}N_2O_2$

Molecular weight	**:**	**170.21**
Chemical name	**:**	**(S)-ethyl-2-oxo-1-pyrolidineacetamide (2S)-(2-oxopyrolidin-1-yl) butanamide**
IUPAC Name	:	(*S*)-2-(2-oxopyrrolidin-1-yl)butanamide
Therapeutic category	**:**	Anticonvulsant.
Description	**:**	White or almost white powder.
Solubility	:	Very soluble in water soluble in acetonitrile. Practically Insoluble in hexane
Dose	**:**	250-1000 mg
Plasma half-life	**:**	6-8 hours
Elimination half life	**:**	5-7 hours for every 8 to 12 hours
Absolute bioavailability	**:**	Approx.100%

PHARMACOLOGY:

Mechanism of action:

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. The antiepileptic activity of levetiracetam was assessed in a number of animal models of epileptic seizures. Levetiracetam did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. Levetiracetam also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. The predictive value of these animal models for specific types of human epilepsy is uncertain.

In vitro and in vivo recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hyper synchronization of epileptiform burst firing and propagation of seizure activity.

Levetiracetam at concentrations of up to 10 μM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepines, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, *in vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated

sodium or T-type calcium currents and levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, *in vitro* studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells.

A saturable and stereoselective neuronal binding site in rat brain tissue has been described for levetiracetam. Experimental data indicate that this binding site is the synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis. Although the molecular significance of levetiracetam binding to SV2A is not understood, levetiracetam and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their antiseizure activity in audiogenic seizure-prone mice. These findings suggest that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic mechanism of action of the drug.

Pharmacodynamics

Effects on QTc Interval

The effect of KEPPRA on QTc prolongation was evaluated in a randomized, double-blind, positive-controlled (moxifloxacin 400 mg) and placebo-controlled crossover study of KEPPRA (1000 mg or 5000 mg) in 52 healthy subjects. The upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc was below 10 milliseconds. Therefore, there was no evidence of significant QTc prolongation in this study.

Pharmacokinetics

Absorption and Distribution

Absorption of levetiracetam is rapid, with peak plasma concentrations occurring in about an hour following oral administration in fasted subjects. The oral bioavailability of levetiracetam tablets is 100% and the tablets and oral solution are bioequivalent in rate and extent of absorption. Food does not affect the extent of absorption of levetiracetam but it decreases Cmax by 20% and delays Tmax by 1.5 hours. The pharmacokinetics of levetiracetam are linear over the dose range of 500-5000 mg. Steady state is achieved after 2 days of multiple twice-daily dosing. Levetiracetam and its major metabolite are less than 10% bound to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.

Metabolism

Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the carboxylic acid metabolite, ucb L057 (24% of dose) and is not dependent on any liver cytochrome P450 isoenzymes. The major metabolite is inactive in animal seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubularreabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function [see Use In Specific Populations and DOSAGE AND ADMINISTRATION].

PREPARATIONS: Tablets (immediate release): 250, 500, 750 and 1000 mg. Tablets (extended release): 500and 750 mg. Oral solution: 100 mg/ml. Injection solution: 100 mg/ml.

STORAGE: Levetiracetam should be stored at 25 C (77 F). Brief storage at 15-30 C (59-86 F) is acceptable.

PRESCRIBED FOR: Levetiracetam is used in combination with other antiseizure medications to treat myoclonic, partial onset, or tonic clonic seizures in children and adults.

DOSING: The recommended daily dose of levetiracetam in adults is 3000 mg. Therapy is initiated with 1000 mg daily (500 mg twice daily) and increased by 1000 mg/day every two weeks up to the maximum recommended dose of 3000 mg/day.

Immediate release tablets, oral solution, and intravenous solutions are administered twice daily, and extended release tablets are administered once daily. The recommended daily dose for children is 60 mg/kg (30 mg/kg twice daily). Therapy is initiated with 20 mg/kg (10 mg/kg twice daily) and increased by 20 mg/kg every two weeks until the recommended daily dose of 60 mg/kg is reached.

DRUG INTERACTIONS: Probenecid (Benemid) reduces the elimination of levetiracetam by the kidneys, potentially doubling the concentration of levetiracetam in the body. This could lead to side effects from probenecid.

PREGNANCY: Levetiracetam has not been adequately studied in pregnant women. Levetiracetam is used during pregnancy only if the benefit justifies the potential risk to the fetus.

NURSING MOTHERS: Levetiracetam is excreted in breast milk. To avoid potential serious side effects in infants who are breastfeeding mothers should consider not breast-feeding while taking levetiracetam.

SIDE EFFECTS: Common side effects associated with levetiracetam includeheadache, sleepiness, weakness, dizziness, and infection. Difficulty walking or moving, hostility, irritability, mood swings, anxiety, hallucinations, and delusions also have been associated with levetiracetam. A small number of patients may experience a decrease in red or white blood cell counts. Like other antiseizure medications, levetiracetam should not be discontinued suddenly because of the risk of increased seizure activity.

Antiepileptic medications have been associated with increased risk of suicidal thinking and behavior. Anyone considering the use of antiepileptic drugs must balance this risk of suicide with the clinical need. Patients who are started on therapy should be closely observed for clinical worsening, suicidal thoughts, or unusual changes in behavior.

Elimination

Levetiracetam plasma half-life in adults is 7 ± 1 hour and is unaffected by either dose or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. The mechanism of excretion is glomerular filtration with subsequent partial tubularreabsorption. The metabolite ucb L057 is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance. Levetiracetam clearance is reduced in patients with impaired renal function [see Use In Specific Populations and DOSAGE AND ADMINISTRATION].

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HYDROXY PROPYL METHYL CELLULOSE

General Descriptions[32]

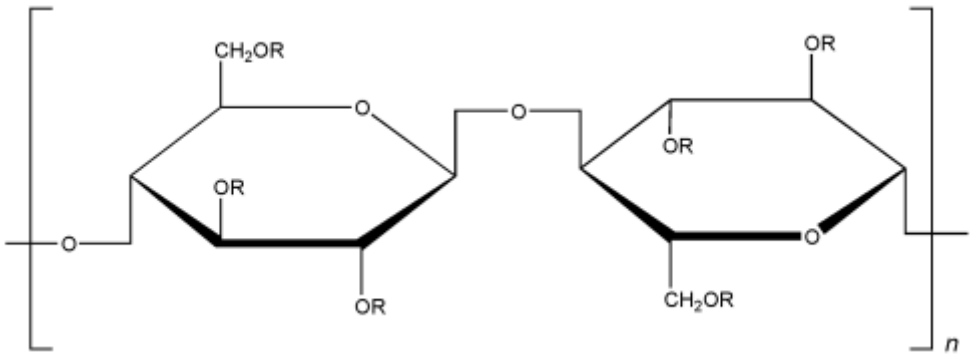
Nonproprietry Names: BP: Hypromellose

USP : Hypromellose

Synonyms : Methocel, HPMC2208, Benecal MHPC, Pharmacoat.

Description : It is odorless & tasteless, white or creamy white colored Fibrous or granular powder.

Structural Formula



Functional categories[32] : Tablet binder, Coating agent, Film former Stabilizing agent, Suspending agent, Viscosity increasing agent.

Solubility : It is soluble in cold water but insoluble in Chloroform, ethanol (95%) & ether but Soluble in mixture of ethanol & dichloromethane mixture of methanol & dichloromethane, mixture of alcohol.

Viscosity (dynamic):

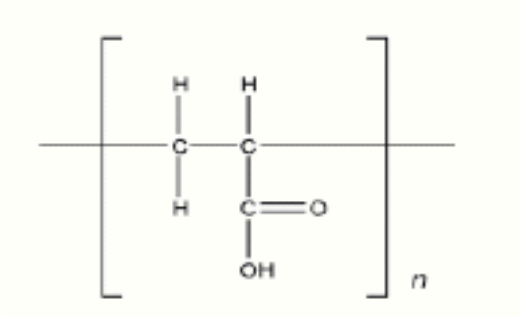
A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols suchas ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.Dichloromethane and ethanol mixtures may also be used to prepare viscous Hypromellose

pH	:	5.5 – 8.0 for a 1 % w/w aqueous solution.
Melting point	:	Brown at 190- 200^{0}C; chars at 225-230^{0}C.
Specific gravity	:	1.26
Loss on drying	:	< 5.0 %
Density (bulk)	:	0.341 gm / cm^3
Density (tapped)	:	0.557 gm / cm^3
Stability and storage Conditions[33]:		Hypromellose powder is a stable material although it is hydroscopic after drying. Solutions are stable at pH 3. Upon heating and cooling hypromellose undergoes a reversible gel transformation. Viscosity of solutions is reduced by increasing the temperature. Depending upon the grade and concentration of material, the gel point is 50-90°C. It is stable material although it is hygroscopic after drying. It should be stored in a well -closed container in a cool dry place.
Incompatibilities	:	Incompatible with some oxidizing Agents.

Applications[34, 35] : It is widely used oral & topical pharmaceutical formulations primarily used in film-coating, binder in tablets in concentrations of 2 – 5 %.

CARBOPOL

Structure:



Carbopol-974, a synthetic high molecular weight, non-linear polymer of acrylic acid cross-linked with polyalkenyl polyether with average molecular weight 3×106 Daltons. It contains not less than 56% and not more than 68% of carboxylic acid (-COOH) groups.

Synonym : Acritamer, Acrylic acid polymer carboxyl vinyl polymer

Non proprietary names:

BP : carbomer,

USP : carbomer

Chemical name : carboxyl polymethylene

Empirical formula : (C_3HO) (-C H -Sucrose)

Category : Bioadhesive, Emulsifying, suspending & viscosity enhancing agent, tablet binder and release-modifying agent.

Description	**:**	white, fluffy, acidic, hygroscopic powder with a slight characteristic odour
Solubility	**:**	After neutralization with alkali hydroxides or amines, soluble in water, in ethanol (96%) and in glycerol.
P^H	:	2.5-3.0 (1% aqueous solution)
Glass transition temperature:		100-105°C
Melting point	**:**	Decomposition occurs within 30 min at 260°C
Specific gravity	:	1.41
Viscosity	**:**	Carbomers disappears in water to form acidic colloidal solutions of low viscosity which when neutralized produce highly viscous gels. 29, 400 to 39,400 cps at 25°C (0.5% neutralized aqueous solution)
Stability and storage	**:**	Carbomers are stable, though hygroscopic materials and can be heated at temperatures below 104°C for up to 2 hours without affecting their thickening efficiency.
Applications	**:**	It is used as thickening, emulsifying and gelling agent. It is used as a tablet binder and matrix \ forming agent in sustained – release formulations affording zero- to near – zero – order release. It is used as the bioadhesive component in mucoadhesive ointments, gels and tablets.

Safety **:** carbomers are regarded as nontoxic and non irritant.

POLYVINYL PYRROLIDINE

1. General discriptions[36].

i.Nonproprietary names

BP : Povidone

USP : Povidone

USP : Polyvidonum

ii. Synonym

Plasdone; PVP; Poly [1-(2-oxo-1-pyrrolidinyl)ethylene]; Polyvidone; 1-vinyl-2-Pyrrolidine polymer.

iii. Chemical Name

1-Ethenyl-2-pyrrolidinone homopolymer;

iv. Emprical Formula

(C_6H_9NO)

v. Molecular Weight

250-3000000

vi. Functional category

Disintegrant; dissolution aid; suspending agent and tablet binder.

2. Applications in Pharmaceutical Formulation or Technology

Polyvinyl pyrrolidine(PVP) is used in a variety of pharmaceutical

- formulations it is Primarily used in solid dosage forms

- In tabletting PVP solutions are used in wet granulation as binders.

- PVP is also added in dry form to the powder blend and granulated in situ by the addition of water, alcohol or viscosity increasing agents in a number of topical and oral suspensions and solutions.

Table no:3

USE	CONCENTRATIONS (%)
Carrier for drugs	10-25
Dispersing agent	Up to 5
Eye drops	2-10
Suspending agent	Up to 5
Tablet binder; tablet	0.5-5
Diluents or coating agent	

3. Description[37]

Polyvinylpyrrolidine is a fine, white to creamy-white colored, odorless or almost odorless and hygroscopic powder.

(i) Properties

Acidity/alkalinity : pH 3.0-7.0 (5% w/v aqueous solution).

Density (true) : 0.409 g/cm^3

Density (tapped) : 0.508 g/cm^3

Density (true) : 1.180 g/cm^3

Melting point : soften at 150°C

Hygroscopicity : it is very hygroscopic. Moisture being absorbed at low Relative humidity.

Particle size : 5% > 200µm in size.

Dynamic viscosity : 10% w/v aqueous solution is 5.5-8.5

5% w/v ethanol is 3.4; 5% w/v on

Propane-2-ol is 5.8.

(ii) Solubility

Freely soluble in acids, chloroform, ethanol, ketones, methanol and water; Practically insoluble in ether, hydrocarbons and mineral oils.

4. Stability and Storage Conditions[38]

PVP darkens to extent on heating at 150ºC with reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110º-130ºC. Steam sterilization of an aqueous solution does not alter its properties.

Since the powder is hygroscopic, it should be stored in an airtight container in a cool and dry place.

LACTOSE, ANHYDROUS

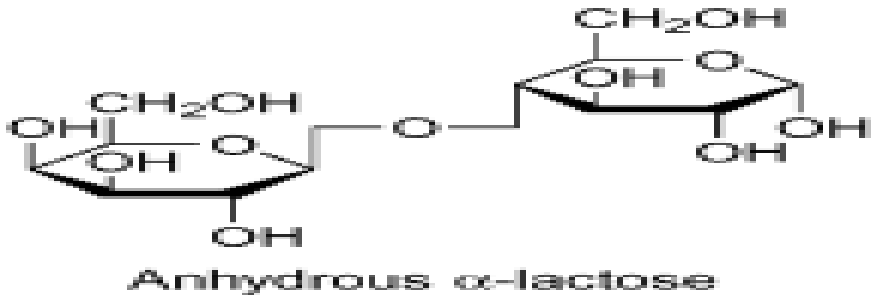
I. Synonyms

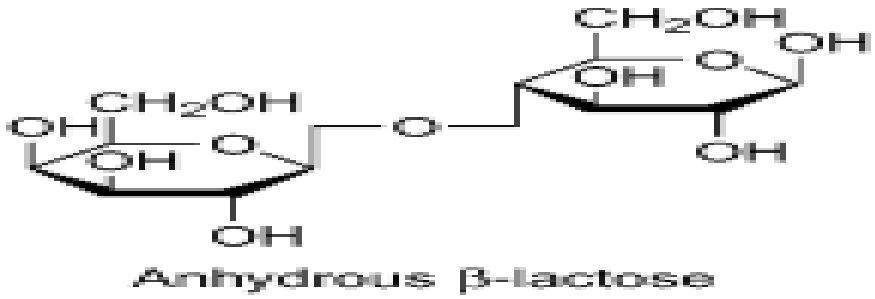
Anhydrous Lactose NF 60M*;* Anhydrous Lactose NF Direct Tableting*; Lacto press Anhydrous; lactosum; lattioso; milk sugar; Pharmatose DCL 21.*

II. Empirical Formula and Molecular Weight

$C_{12}H_{22}O_{11}$ 342.30.

III. Structural Formula





IV. Functional Category

Binding agent; directly compressible tableting excipient; lyophilization aid; tablet and capsule filler.

V. Description

Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α-lactose. Anhydrous lactose typically contains 70–80% anhydrous β-lactose and 20–30% anhydrous α-lactose.

Loss on drying ≤.05%

Angle of repose:

39° for *Pharmatose DCL 21* and 38° for *Super-Tab Anhydrous.*

Density (true):

1.589 g/cm^3 for anhydrous β-lactose; 1.567 g/cm^3 for *Super-Tab Anhydrous*.

Density (bulk):

0.68 g/cm^3 for *Pharmatose DCL 21*; 0.67 g/cm^3 for *Pharmatose DCL 22*; 0.65 g/cm^3 for *Super-Tab Anhydrous*.

Density (tapped):

0.88 g/cm^3 for *Pharmatose DCL 21*; 0.79 g/cm^3 for *Pharmatose DCL 22*; 0.87 g/cm^3 for *Super-Tab Anhydrous*.

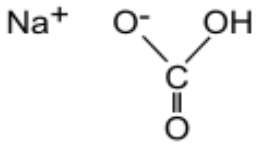
Solubility: Soluble in water; sparingly soluble in ethanol (95%) and ether.

VI. Applications in Pharmaceutical Formulation or Technology

Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.

SODIUM BICARBONATE

Structure:



Sodium bicarbonate natural mineral form is nahcolite. It is a component of the mineral natron and is found dissolved in many mineral springs. It is found in dissolved form in bile, where it serves to neutralize the acidity of the hydrochloric acid produced by the pancreas, and is excreted into the duodenum of the small intestine via the bile duct. It is also produced artificially.

IUPAC name	:	Sodium hydrogen carbonate
Other names	:	Baking soda, bicarbonate of soda, break soda, sodium bicarbonate, E500,
Functional category	:	alkalizing agent, Therapeutic agent
Molecular formula	:	$NaHCO_3$
Molar mass	:	84.01 g mol^{-1}
Density	:	2.173 g/ cm
Melting point	:	50 °C, 323 K, 122 °F (decomposes)
Boiling point	:	851 °C, 1124 K, 1564 °F
Solubility	:	Insoluble in ethanol and ether, soluble in water – 9 g/100 mL, 69 g/L (0 °C), 96 g/l (20 °C), 165 \ g/l (60 °C), 236 g/L (100 °C)
Acidity (pK_a)	:	10.329- 6.351 (carbonic acid)
Refractive index	:	1.3344
Routes of administration	:	Intravenous, oral
Description	:	Sodium bicarbonate is a white solid that is crystalline, odourless, but often appears as a fine powder. It has a slightly salty, alkaline taste resembling that of washing soda (sodium carbonate).

Chemistry: Sodium bicarbonate is an amphoteric compound. Aqueous solutions are mildly alkaline due to the formation of carbonic acid and hydroxide ion:

$$HCO3 + H_2O \rightarrow H_2CO_3 + OH^-$$

Sodium bicarbonate can be used as a wash to remove any acidic impurities from a "crude" liquid, producing a purer sample. Reaction of sodium bicarbonate and an acid produce a salt and carbonic acid, which readily decomposes to carbon dioxide and water:

$NaHCO_3 + HCl \rightarrow NaCl + H_2CO_3$

$H_2CO_3 \rightarrow H_2O + CO_2\,(g)$

Sodium bicarbonate reacts with acetic acid (found in vinegar), producing sodium acetate, water, and carbon dioxide:

$NaHCO_3 + CH_3COOH \rightarrow CH_3COONa + H_2O + CO_2(g)$

Sodium bicarbonate reacts with bases such as sodium hydroxide to form carbonates:

$NaHCO_3 + NaOH \rightarrow Na_2CO_3 + H_2O$

Sodium bicarbonate reacts with carboxyl groups in proteins to give a brisk effervescence from the formation of CO_2. This reaction is used to test for the presence of carboxylic groups in protein.

Pharmaceutical applications:

It is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules it is also used in tablet formulations to buffer drug molecules that are weak acids, thereby increasing the rate of tablet dissolution and reducing gastric irritation. Recently, sodium bicarbonate has been used as a gas forming systems and in floating oral controlled release oral dosage forms of furosemide and cisapride.

- Disintegrating agent
- Neutralizing acids and alkalis
- In cooking
- As antacid in medicine
- Cleaning agent

Stability and storage conditions:

Sodium bicarbonate powder is stable below 76% relative humidity at 25°C and below 48% relative humidity at 4°C. Aqueous solutions of Sodium bicarbonate may be sterilized by filtration or autoclaving. To minimize decomposition of Sodium bicarbonate by decarboxyation autoclaving, carbon dioxide is passed through the solution in its final container, which is than hermetically sealed and autoclaved aqueous solutions of sodium bicarbonate stored in glass containers may develop deposits of small glass particles. Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in a well closed container in a cool and dry place.

Incompatibilities:

Sodium bicarbonate reacts with acids, acidic salts, and many salts, with the evolution of carbon dioxide.

TALC

1. **Non-Proprietary names:**
   - **BP:** Purified talc
   - **JP:** Talc
   - **USP:** Talc

2. **Synonyms:** Hydrous magnesium calcium silicate, hydrous magnesium silicate, magnesium hydrogen meta silicate, powdered talc, purified French chalk, soapstone.
3. **Chemical name and CAS registry number:** Talc [14807-96-6]
4. **Emperical formula and molecular weight:** Talc is a purified hydrated magnesium silicate, approximating to the formula $Mg_6 (Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminium silicate and iron.
5. **Functional category:** Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.
6. **Applications in pharmaceutical formulations and technology:**

Table No: 4

S.no	Use	Concentration (%)
1.	Dusting powder	90.0-99.0
2.	Glidant and tablet lubricant	1.0-10.0
3.	Tablet and capsule diluents	5.0-30.0

7. **Description:** It is a very fine, white to grayish-white, odourless, impalatable, unctuous, crystalline powder**.** It adheres readily to the skin and is soft to touch and free from grittiness.
8. **Typical properties:**

Acidity/alkalinity : 7-10 for a 2-% w/v aqueous dispersion

Hardness **:** 1.0-1.5

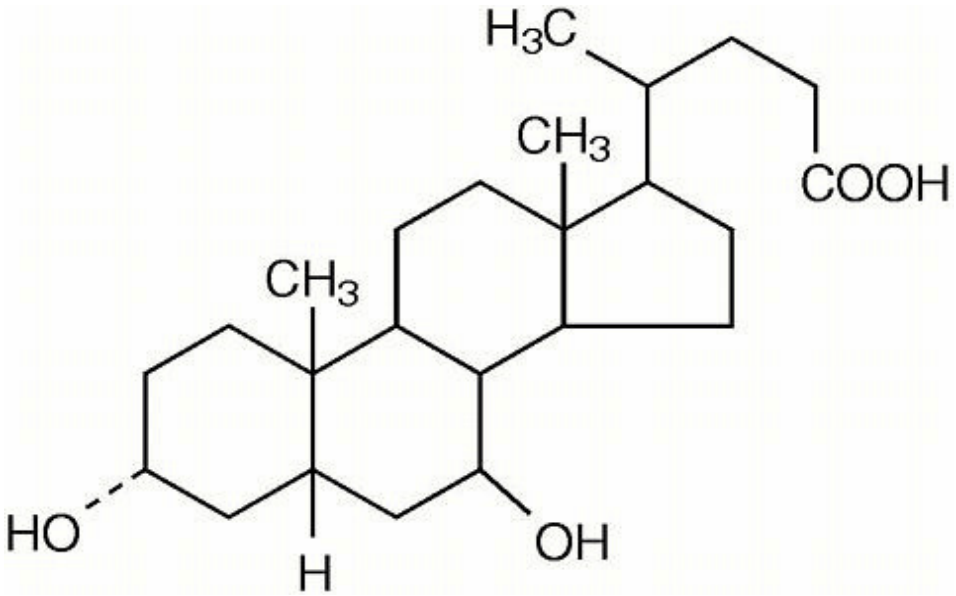
Solubility **:** Insoluble in dilute acids and alkalis, organic solvents and water.

MAGNESIUM STERATE

Synonyms **:** magnesium octadecanoate, stearic acid magnesium salt

Empirical formula : $C_{36}H_{70}MgO_4$

Structure:



Molar mass : 591.34

Functional category : Tablet and capsule lubricant

Description : Magnesium Stearate is a fine; white precipitated or milled impalpable powder with low bulk density. The powder is greasy to touch and readily adhere to skin.

Bulk density : 0.159 gm/cm

Tapped density : 0.286 gm/ cm

True density : 1.092 gm/cm

Solubility : Slightly soluble in warm ethanol (95%); practically insoluble in ether, and water.

Melting range : 117-150

Applications in pharmaceutical formulation

It is widely used in cosmetics, foods and pharmaceutical formulations. Primary use is as a lubricant in capsule and tablet manufacturing at concentration between 0.25 – 5.0%.

Storage conditions: Store in a well closed container in a cool & dry place.

Incompatibility: Magnesium stearate is incompatible with strongacids, alkalis and iron salts. It cannot be used in products containing most alkaloidal salts. Aspirin, certain vitamins and most alkaloidal salts.

Safety: It is widely used as a pharmaceutical excipient and is regarded as non-toxic for oral administration. Oral consumption in large amount may result in laxative effect or mucosal irritation.

Handling precautions: Eye protection and hand gloves are recommended. Magnesium stearate should be handled in a well- ventilated environment, a respirator mask is recommended.

METHODOLOGY

1. Formulation of Levetiracetam floating tablets using different polymers: HPMC K4M, HPMC E15, Carbopol 974 p, Sodium Bicarbonate, Magnesium stearate and Talc in different ratios.
2. FTIR absorption studies have also been carried out for the pure drug and for drug polymer.
3. Compression of the powders into floating tablets of Levetiracetam. Evaluation of floating tablets of Levetiracetam for physical appearance, hardness, thickness, friability, weight variation, content uniformity test, and in-vitro buoyancy studies.
4. *In vitro* dissolution studies for all the formulations of levetiracetam floating tablets.

Materials

A. Procurement of Drug and Excipients:

The following materials and instruments used in the experiment are of laboratory grade.

Table No 5: Details of materials used:

Name of the materials	Manufacturer
Levetiracetam	Divi's Laboratories ltd Andhra Pradesh India.
HPMC K4M	TAITAN RUITAI Cellulose.co.,ltd.P.R.China
HPMC E15	TAITAN RUITAI Cellulose. co.,ltd.P.R.China
CARBOPOL 974 p	Corel pharma chem., gujarat, india.
PVP K30	Nanhang industrial co.,ltd.
Sodium bi carbonate	Finar Chemicals Limited, Ahmedabad, India.
Lactose	Loba Chemie Pvt.Ltd, Mumbai, India.
Talc	Kemphasol, Mumbai, India
Magnesium stearate	S.d.fine-Chem Ltd. Mumbai, India

B. INSTRUMENTS AND EQUIPMENTS USED

Table No 6: Details of equipment used

INSTRUMENTS

S. NO	INSTRUMENTS / EQUIPMENTS	MODEL AND MANUFACTURER / SUPPLIER
1.	Digital Balance	Shimadzu AX-200 corporation, Japan
2.	Electronic Balance	Schimadzu corporation, Japan
3.	UV-Visible Spectrophotometer	UV-1700 Shimadzu corporation, Japan
4.	Rotary compression machine	Cadmach, india.
5.	Friabilator	EF-2 Friabilator, Electro lab, Mumbai
6.	Hardness tester	Pfizer hardness tester, Servewell instruments and equipments Pvt. Ltd., Bangalore.
7.	Dissolution apparatus	Electrolab TDT 08 Dissolution tester USP
8.	Digital pH meter	7007, Digisun electronics, Hyderabad
9.	Glass ware	Borosil, Chennai.
10	FTIR	Shimadzu, japan

6.2 METHODS

6.2.1 Analytical Study

UV Spectroscopic method for analysis of Levetiracetam:

Preparation of 0.1 N Hydrochloric acid:

8.5ml of Concentrated HCl was taken in a volumetric flask and it was made up to 1000ml with distilled water.

Preparation of Stock solution

Weighed accurately 100mg of Levetiracetam pure drug was dissolved in 100ml of 0.1N HCL (stock solution) (1000µg/ml).10ml of solution was taken and make up with100ml of 0.1N HCL (100µg/ml).

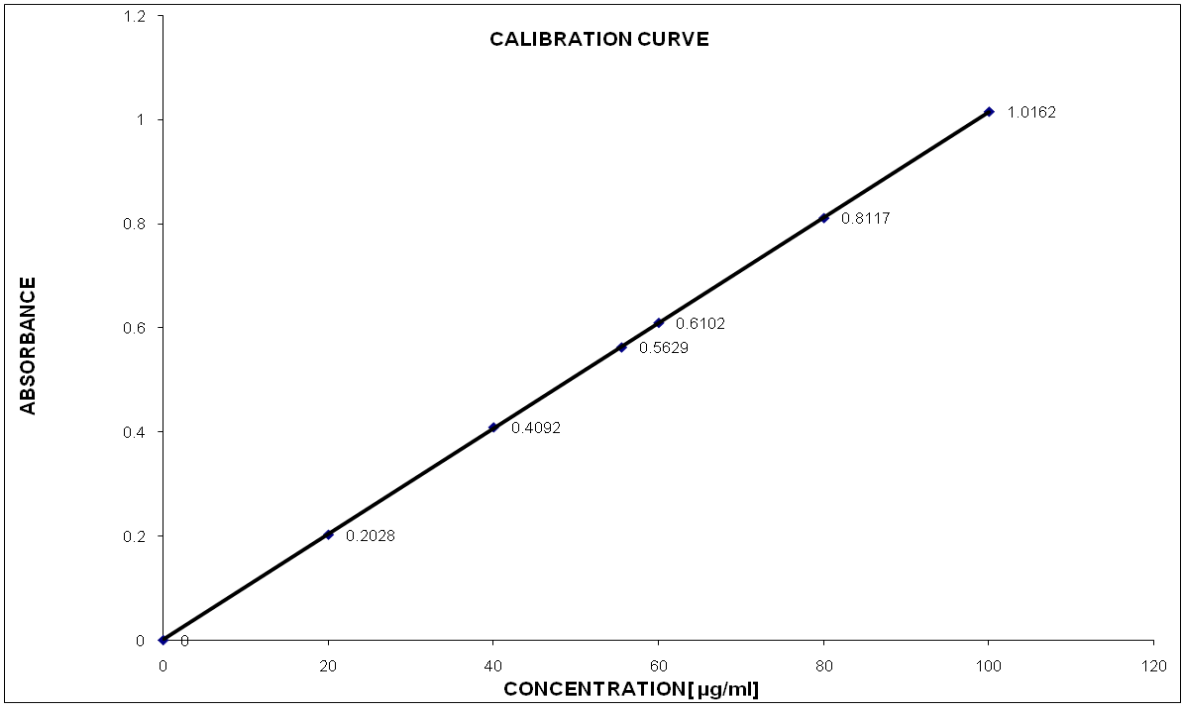
Preparation of Standard solution

The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions containing 20,40,60,80 and 100µg/ml of Levetiracetam per ml of solution.

- The absorbance of the above dilutions was measured at 210 nm by using UV-Spectrophotometer taking 0.1N HCl as blank.
- Then a graph was plotted by taking concentration on X-Axis and absorbance on Y-axis which gives a straight line.

Table No 7: Calibration curve of Levetiracetam in 0.1N HCl (p^H1.2) λ_{max} 210 nm

S.no.	Concentration (µg/ml)	Absorbance
1	0	0
2	20	0.2028
3	40	0.4092
4	55.5	0.5629
5	60	0.6102
6	80 0.8117	
7	100	1.0162



PREFORMULATION STUDY

6.3. PREFORMULATION

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms. Preformulation studies relate to pharmaceutical and analytical investigation carried out in supporting formulation development efforts of the dosage form. The following Preformulation studies were performed for the obtained sample of drug.

6.3.1. Physical characteristics:

6.3.1.1. Flow properties: [39]

The flow properties of powders are critical for an efficient tabletting operation. A good flow of powder or granulation to be compressed is necessary to assure efficient missing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the pre formulation stage to be "poorly flowable", the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be pre-compressed or granulated to improve their flow properties. During pre formulation evaluation of drug substance, therefore, its flowability characteristic should be studied, especially when the anticipated dose of the drug is large. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Procedure:

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction.

The height of the heap was measured by using scale. The values of angle of repose are calculated by using the following formula:

Tan θ = h/r

$\theta = \tan^{-1}$ (h/r)

Where, θ – angle of repose

h- Height of the heap

r - Radius of the heap

Table No 8: Angle of repose limits

Angle of repose	Flowability
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

The results are shown in Table 14.

6.3.1.2 Bulk density

Bulk density is the ratio of mass of powder to the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder.

Procedure:

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume. Calculate the bulk density, in gm per ml, by the formula

$(\rho_b) = m / V_b$.

Where, ρ_b =Bulk Density

m = mass of powder

V_b = initial / bulk volume

The results are shown in Table 14.

6.3.1.3. Tapped density:

Tapped density is the ratio of mass of powder to the tapped volume.

Procedure:

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. Calculate the tapped density, in gm per ml, by the formula:

$(\rho_t) = m/V_t$

Where, ρ_t =Tapped Density

m = mass of powder

V_t= final / tapped volume

6.3.1.4 Measurement of Powder Compressibility:

Compressibility Index is measure of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free flowing powder, such interactions are generally less and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater inter particle interactions, and a greater difference between bulk and tapped densities will be

observed. These differences are reflected in the compressibility Index Calculated by the formula,

$$\% \text{ Compressibility (Carr's index)} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

Table No 9: Compressibility index limits

%Compressibility	Flowability
5-12	Excellent
12-16	Good
18-21	Fair
23-25	Poor
33-38	Very poor
more than 40	Very, very poor

6.3.1.5 Hausner's Ratio:

It is the ratio of volume of tapped volume or tapped density to bulk density

Hausner's Ratio = Vb/Vt or ρ_t / ρ_b.

Table No 10: Hausner's Ratio index limits.

Hausner's Ratio	Flowability
1.2-1.3	Excellent
1.3-1.4	Good
1.4-1.5	Fair
1.3-1.4	Poor

6.4. Identification of drug and compatibility study:

6.4.1. Drug - Excipient Compatibility Studies [40]

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-

excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the pre formulation scientist must generate the needed information.

By Physical observation

It was determined as per procedure given in method section. The following table illustrated the result.

Table No 11: Physical Compatibility Studies

Test	Observations	Inference
Physical compatibility	No change of color	These materials are compatible for formulations.

Procedure by IR Studies [41,42]

The IR spectrums of the Levetiracetam with excipients were taken by preparing dispersion in dry potassium bromide under dry condition. Obtained spectra were superimposed. The transmission minima (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the standards.

6.5 Preparation of tablets

Preparation of levetiracetam Floating Tablets

Twelve formulations of floating tablets of levetiracetam using the polymer of different grades namely Hydroxy Propyl Methyl Cellulose K4M (HPMC K 4 M), and Hydroxy Propyl Methyl Cellulose E15 (HPMC E15) in different concentrations were prepared by wet granulation method. Sodium bicarbonate was used as a gas

generating agent. Polyvinyl Pyrrolidine (PVP K30) is used as solubilizer enhancing agent. Lactose is used as a diluent.

Twelve formulations of levetiracetam were prepared. Pure levetiacetam, sodium bicarbonate, HPMC K4M, HPMCE15 and carbopol 974P with different concentrations, Polyvinyl Pyrrolidone (PVP K30), sodim bicarbonate and lactose were mixed together in mortar and pestle to get uniform mixture. Now the blended powder was passed through sieve no. 60. Granules were prepared using isopropyl alcohol as a solvent. Prepared granules were dried at tray drier. After drying the granules were passed through sieve no; 22. The dried granules was subjected to different preformulation studies namely Bulk density, Tapped Density and Angle of Repose. After that the granules was mixed with talc and magnesium stearate uniformily and then compressed into tablets by compression.All the formulations were prepared by wet granulation method. The compressions of different formulations are given in Table -The tablets were prepared as per the procedure given above and the aim is to controlled the release of Levetiracetam floating tablets.

Table No 12: Composition of gastro-retentive tablets of Levetiracetam (in mg)

Ingrediants	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Levetiracetam	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K4M	50	100	50	50	50	50	----	----	50	50	50	----
HPMC E15	150	150	200	150	150	150	150	150	0	0	----	----
Carbopol 974 p	----	----	0	0	0	----	100	150	100	150	150	150
Sodium Bi Carbonate	100	100	100	50	100	150	100	100	100	100	100	100
Lactose	0	0	0	0	100	0	0	0	0	0	100	0
PVP k30	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10	10	10	10

Total weight	815	865	865	765	915	865	865	915	765	815	915	765

6.6. EVALUATION OF TABLETS

The formulated tablets were evaluated for the following physicochemical characteristics:

6.6.1 General appearance:

The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture and odor.

6.6.2 Hardness test: [43]

Hardness of the tablet was determined by using the Monsanto hardness tester (n=3or5) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

6.6.3 Thickness of tablets

The tablets should have uniform thickness. Thickness was measured by using vernier calipers. To get required thickness before compression these values are checked and adjusted.

6.6.4 Weight variation[44]:

20 tablets were selected at random and weighed individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not.

6.6.5 Uniformity of weight:

The values of average weight are given in below the table 10 and are in within limit Percentage

Sr. No	Average weight of tablet	Percentage of deviation
1	<80mg	10
2	80 – 250 mg	7.5
3	>250mg	5

$$\text{Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Table No.13

6.6.7 Friability test: [45]

20 previously weighed tablets were placed in the apparatus. Which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,

Percentage friability = (initial weight - final weight) / initial weight × 100.

6.6.8 Drug content: [46]

Twenty tablets of each formulation were weighed, powdered about 100mg equivalent levetiracetam was transferred into a 100ml volumetric flask and the volume was made up with 0.1N HCL. A suitable volume of this was then diluted with 0. 1N HCL to get a appropriate concentration, then filtered through 0.45 μm whatmann filter paper, the absorbance of resulting solution was analysed by UV-Visible spectrophotometer at a maximum of about 210nm using 0.1N HCL as blank solution.

5.6.9 *In vitro* Buoyancy studies: [47,48]

The buoyancy tablet was studied at 37±0.5^{0}c. The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface of the liquid to float was determined as the Buoyancy Lag Time (BLT) or Floating Lag Time (FLT) and the duration of time of the tablet constantly floating on the dissolution medium was noted as total floating time (TFT).

5.6.10 Buoyancy Determination[49]

i. Buoyancy Lag Time (BLT) :- The time interval between the introduction of Levetiracetam floating tablets in to the dissolution medium and its flotation to the top of dissolution medium was termed as BLT.

BLT may be explained as a result of time required for dissolution medium to penetrate the tablet and develop the swollen layer for the entrapment of CO_2 generating in situ. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the tablet.

ii. Duration of Buoyancy (DB):- The duration upto which the dosage form floats over the dissolution medium was termed as DB.

Duration of buoyancy of tablet depends on the amount of sodium bicarbonate involved in CO_2 formation, for a floating system. In order to intiate rapid generation of CO_2 and allowed to release CO_2 to promote floating, the ideal tablet of coating material should be highly permeable.

Method : The buoyancy lag time and duration of buoyancy were carried using USP 24 type II dissolution apparatus in 900 ml of 0.1N Hcl at 37 ± 1 ^oC

vii) swelling index[50]

The swelling index studies were carried out in petri dishes using simulated gastric fluid (pH 1.2).The randomly selected tablets from each formulation were weighed individually (W_0) and placed separately in 50 ml of simulated gastric fluid (pH 1.2) in petri dish. After 8 hours swollen tablet was removed from the medium the excess water was blotted with filter paper and immediately weighed (w_1). The swelling index (SI), expressed as a percentage and was calculated from the following equation

$$SI = \frac{W_1 - W_2}{W_0} \times 100$$

5.7 *IN VITRO* DISSOLUTION STUDIES OF TABLETS:

5.7.1 Dissolution parameters:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl (p^H 1.2)
RPM	--	50 rpm
Temperature	--	37°c $\pm$ 0.5°C

5.7.2 Dissolution Study:

The floating tablets were evaluated for dissolution rate in 0.1 N HCl (p^H 1.2).

Procedure: [51]

The release of levetiraceatm from the tablets was studied by using USP 29 paddle apparatus. Drug release profile was carried out in 900ml of freshly prepared 0.1N HCL maintained at 37 ± 0.5ºC as a medium and rotating the paddles at 50rpm. At each sampling interval, 10 ml of the sample was withdrawn and replaced by an equal volume of 0.1 N HCl. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by using UV spectrophotometer. The absorbance of the sample solution was measured at the maximum wavelength of 210 nm. Cumulative percentage of drug release was calculated using the equation obtained from the standard curve.

The present study was to formulate Levetiracetam floating tablets in twelve different batches F1 to F12 using polymer Hydroxy propyl methyl cellulose of two different grades (HPMC K15 M and HPMC K4 M) and carbopol 974 p in different concentrations. All the formulations were prepared by wet granulation method. The granules were subjected to IR spectral analysis. The granules were taken for preformulation studies such as Bulk density, Tapped density, Angle of repose, Compressibility index and Hausner ratio and tabulated in table no 14. After compression, evaluation tests of tablet such as hardness, weight variation, friability, buoyancy determination, swelling index and content uniformity is done. Finally the tablets were evaluated for invitro-drug release.

Evaluation of levetiracetam granules

Bulk density

By using measuring cylinder the bulk density of all formulations was measured. The bulk density was found in the range of 0.3236-0.3867. It is within the acceptable limits.

Tapped density

Tapped density of all formulations measured by measuring cylinder and values were determined. The tapped density was found in the range of 0.3905-0.4724 gm/cm^3. It showed that tapped density is within the acceptable limit.

Angle of Repose

For all the formulations angle of repose were found within 30.24^0, granules indicates good flow property. The results showed that the flow properties of all formulations are good 22.41^0 to 30.24^0

Compressibility Index

The granules show good flow character, since the compressibility index of all the formulation is between 11-15.

Hausner Ratio

Hausner ratio of all the formulations were between 1.12-1.18. If the Hausner ratio lies between 1.13-1.27, it indicates good flow behavior of the granules or powder. The results indicates the granules possess good flow property.

BATCH NO	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (I_C)	Hausner ratio (H_R)	Angle of repose
F1	0.3423	0.4156	12.14	1.21	25.40°
F2	0.3684	0.4226	11.47	1.14	28.82°
F3	0.3354	0.3905	11.64	1.26	26.7°
F4	0.3741	0.4724	12.62	1.18	29.84°
F5	0.3566	0.4241	11.89	1.18	22.41°
F6	0.3654	0.4421	12.09	1.120	24.25°
F7	0.3346	0.4133	12.35	1.23	28.48°
F8	0.3542	0.4491	12.67	1.26	26.92°
F9	0.3285	0.4198	12.77	1.27	30.24°
F10	0.3236	0.4165	12.12	1.21	29.82°
F11	0.3398	0.3956	11.64	1.16	24.56°
F12	0.3867	0.4379	11.32	1.13	22.48°

Table no:14

Evaluation of Levetiracetam Floating Tablets

The evaluated levetiracatm Floating tablets were evaluated and the results are shown in table no15.

- The hardness of the tablets were tested by using Mosanto hardness tester, and the results are tabulated in the Table-15. The hardness of the tablets of all formulations were within the range of 4.0-4.8 Kg/cm^2.
- Tablet mean thicknesses were almost uniform in all formulations and were found to be in the range of 3.38 to 3.79mm. (Table no15.)
- Friability value was found to be less than 1% and considered to be satisfactory.(Table no15.)
- All this tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values.(Table no15.)
- Drug content was within the acceptable range which shows the proper mixing of the drug with the excipients.
- Swelling Index: Swelling Index of the polymers can be measured by their ability to absorb water and swell enormously. Swelling Index is within the range of 51.17-96.23%

Table no:15

Batch no	Average wt	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Swelling index	Drug content

	(mg)				(%)	(%)
F1	816±1.14	3.5±0.04	4.5±0.02	0.28%	52.24%	98.26%
F2	864±0.70	3.6±0.06	4.2±0.08	0.3%	88.03%	99.08%
F3	866±0.83	3.7±0.04	4.5±0.02	0.25%	72.93%	97.96%
F4	763±1.14	3.39±0.01	4±0.07	0.21%	63.94%	101.17%
F5	912±1.16	3.79±0.08	4.7±0.015	0.32%	65.41%	98.48%
F6	866±0.83	3.71±0.01	4.5±0.20	0.2%	61.48%	98.74%
F7	868±1.14	3.7±0.04	4.5±0.20	0.25%	76.58%	98.53%
F8	914±0.83	3.77±0.01	4.8±0.15	0.28%	85.11%	100.07%
F9	763±0.89	3.4±0.04	4.1±0.05	0.22%	73.56%	99.24%
F10	814±0.83	3.5±0.04	4.3±0.13	0.26%	51.17%	97.41%
F11	912±0.83	3.78±0.01	4.5±0.20	0.29%	96.23%	96.84%
F12	768±1.30	3.38±0.01	4.3±0.07	0.24%	77.00%	98.74%

Buoyancy Determination

i) Buoyancy Lag Time (BLT) :

Buoyancy lag time were determined by using dissolution apparatus at 50 rpm using 900ml pH 1.2 buffer and temperature was maintained at 37^0C ± 0.5^0C throughout the study. The Buoyancy Lag Time is in between 40-780 sec for all formulations. F6 alone had buoyancy lag time more than 15 minutes.

ii) Duration of Buoyancy (DB):

Duration of buoyancy (DB) is the time that the tablet floats in the dissolution medium. Duration of Buoyancy (DB) of all the formulations is more than 12 hours, except F12, F8 and F7.

Table no:16

FORMULATION	BUOYANCY LAG TIME (SEC.)	DURATION OF BUOYANCY(Hrs.)
F1	540 Sec	>12
F2	600 Sec	>12
F3	624 Sec	>12
F4	240 Sec	>12

F5	600 Sec	>12
F6	1500 Sec	>12
F7	780 Sec	<12
F8	780 Sec	<12
F9	40 Sec	>12
F10	60 Sec	>12
F11	560 Sec	>12
F12	120 Sec	<12

INFRARED SPECTRAL STUDIES

The results of the IR spectra studies are presented in figure 1,2,3,4,5,6,7.

The IR spectrum of drug-polymer shows that there is no specific interaction between Levetiracetam and hydroxyl propyl methyl cellulose (HPMCK4M &E15),and Carbopol 974p.

The primary amino group(NH_2) peak of levetiracetam is seen clearly at around 3360 cm^{-1} in the spectra of mixed formulations.

The C-N Heterocyclic peak is observed at 2360cm^{-1} in both levetiracetam spectra and spectra of mixed formulation.

Based on the above IR spectra, there is no significant interaction between drug & polymer as evidenced by the presence of bonds due to the responding reactive functional groups.

DISSOLUTIONS STUDIES

The Dissolution rate studies were performed to evaluate the dissolution characteristic of levetiracetam from floating tablets with twelve formulations were prepared. The drug release of twelve formulations were compared with each other. The results are presented in table 17 to 28 . From the invitro drug release studies the T50% T70% T90% were calculated and the results were depicted in the table no29.

Cumulative percentage of drug release from the tablets

Table no:17

Time	FORMULATION -1
0	0
1 hr	11.45%
2 hrs	23.35%
3 hrs	29.45%
4 hrs	38.76%
5 hrs	45.25%
6 hrs	52.55%
7 hrs	59.85%
8 hrs	64.75%
9 hrs	72.23%
10hrs	79.45%
11hrs	84.25%
12hrs	93.5%

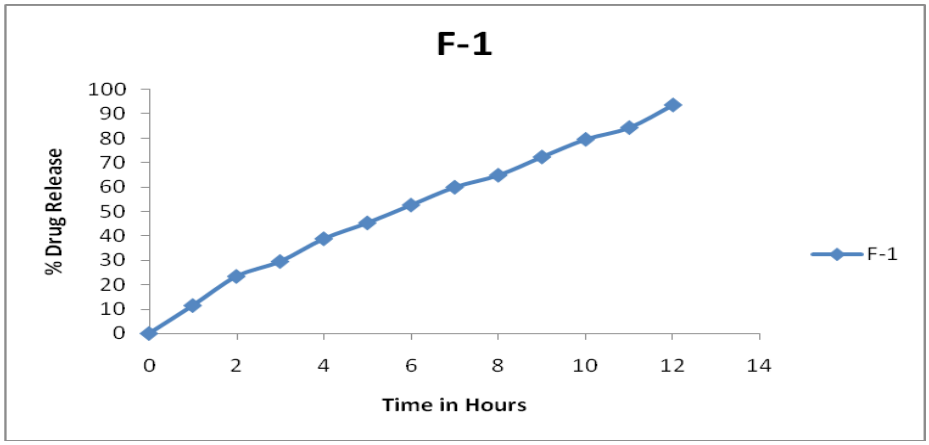


Fig. : Percent Drug Released Vs Time Plots of formulations F 1

Table no:18

TIME	FORMULATION -2
0	0
1 hr	13.25%
2 hrs	20.98%
3 hrs	26.51%
4 hrs	31.96%
5 hrs	37.65%
6 hrs	44.12%
7 hrs	53.75%
8 hrs	59.92%
9 hrs	67.85%
10hrs	72.35%
11hrs	78.16%
12hrs	84.7%

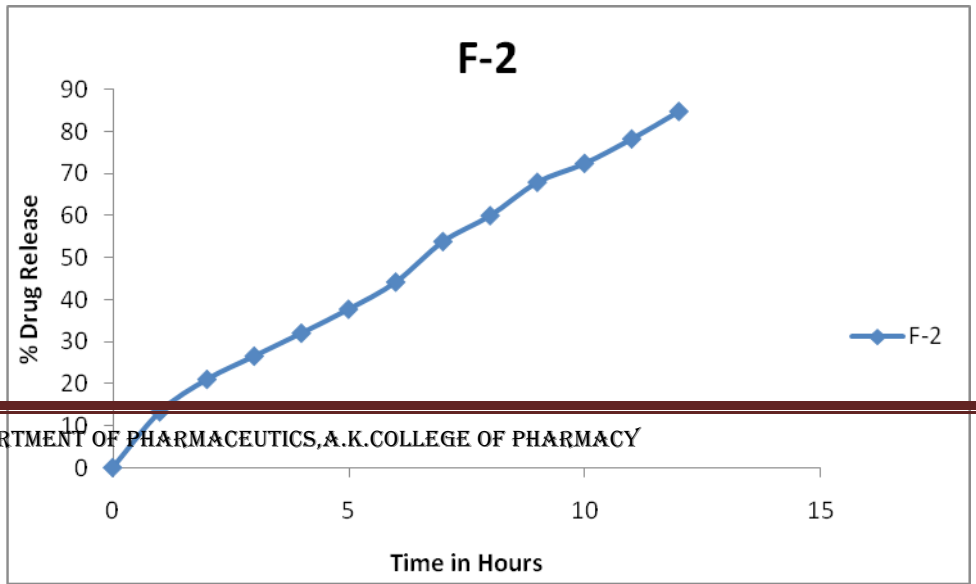


Fig. : Percent Drug Released Vs Time Plots of formulations F 2

Table no:19

TIME	FORMULATION -3
0	0
1 hr	23.13%
2 hrs	31.06%
3 hrs	42.16%
4 hrs	49.59%
5 hrs	55.23%
6 hrs	60.95%
7 hrs	64.72%
8 hrs	70.79%
9 hrs	74.65%
10hrs	78.3%
11hrs	81.45%
12hrs	86.75%

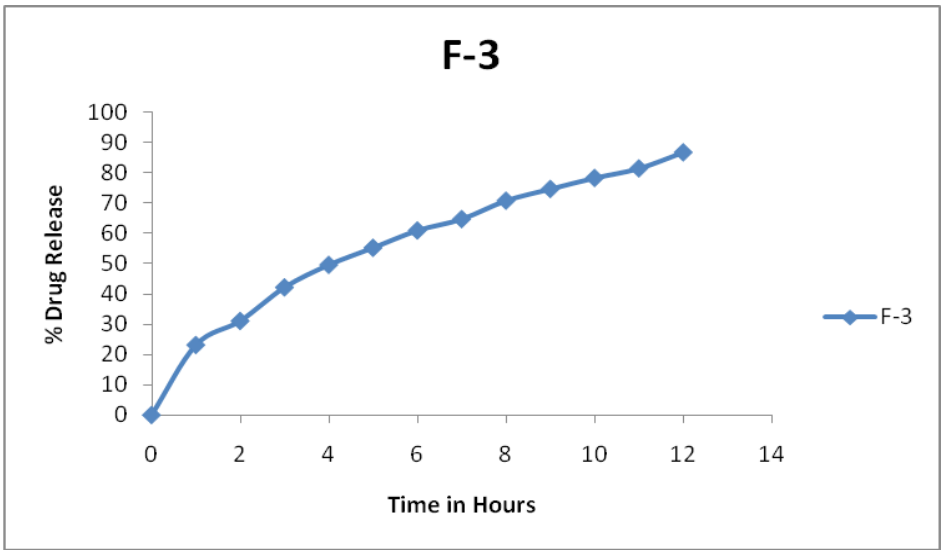


Fig. : Percent Drug Released Vs Time Plots of formulations F 3

Table no:20

TIME	FORMULATION -4
0	0
1 hr	9.55%
2 hrs	19.9%
3 hrs	25.48%
4 hrs	31.65%
5 hrs	38.25%
6 hrs	46.45%
7 hrs	49.25%
8 hrs	56.18%
9 hrs	62.55%
10hrs	69.85%
11hrs	79.7%
12hrs	88.55%

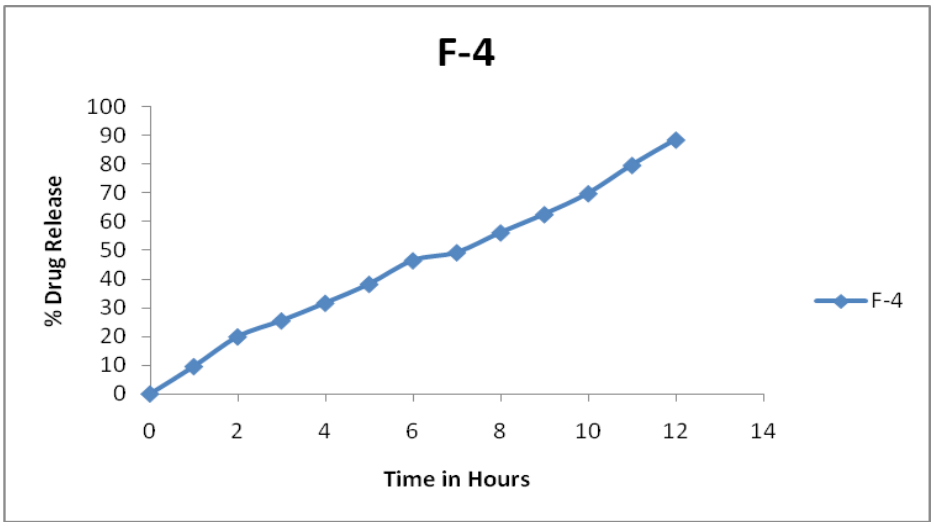


Fig. : Percent Drug Released Vs Time Plots of formulations F 4

Table no:21

TIME	FORMULATION -5
0	0
1 hrs	8.56%
2 hrs	15.6%
3 hrs	27.32%
4 hrs	39.75%
5 hrs	56.32%
6 hrs	61.2%
7 hrs	67.38%
8 hrs	74.6%
9 hrs	78.72%
10hrs	83.68%
11hrs	89.25%
12hrs	95.05%

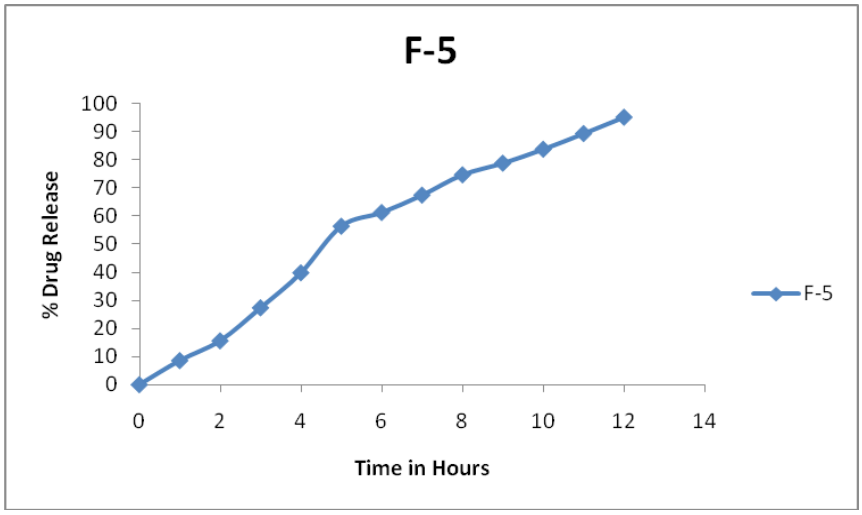


Fig. : Percent Drug Released Vs Time Plots of formulations F 5

Table no:22

TIME	FORMULATION -6
0	0
1 hrs	10.16%
2 hrs	21.58%
3 hrs	27.45%
4 hrs	33.42%
5 hrs	49.48%
6 hrs	54.48%
7 hrs	61.25%
8 hrs	68.58%
9 hrs	76.95%
10hrs	82.35%
11hrs	88.75%
12hrs	94.8%

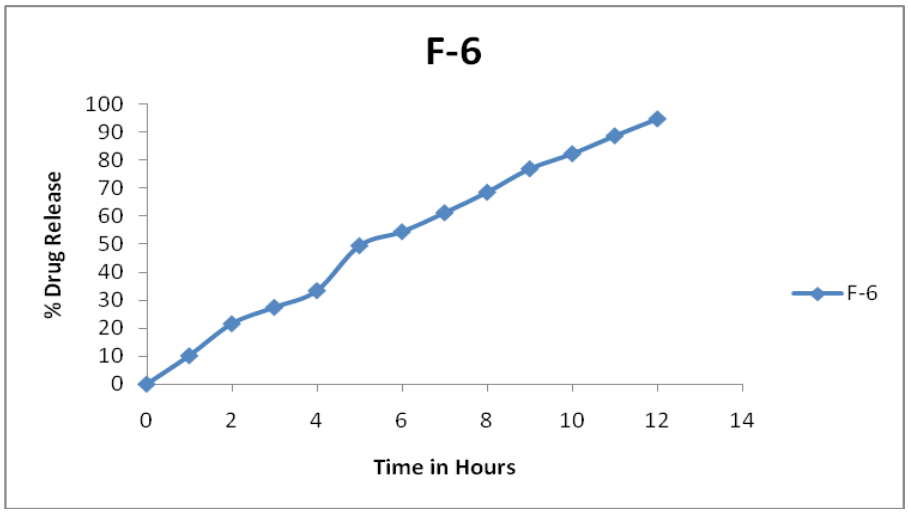


Fig. : Percent Drug Released Vs Time Plots of formulations F 6

Table no:23

TIME	FORMULATION -7
0	0
1 hrs	39.87%
2 hrs	48.73%
3 hrs	57.82%
4 hrs	67.76%
5 hrs	77.65%
6 hrs	84.96%
7 hrs	98.92%
8 hrs	-
9 hrs	-
10hrs	-
11hrs	-
12hrs	-

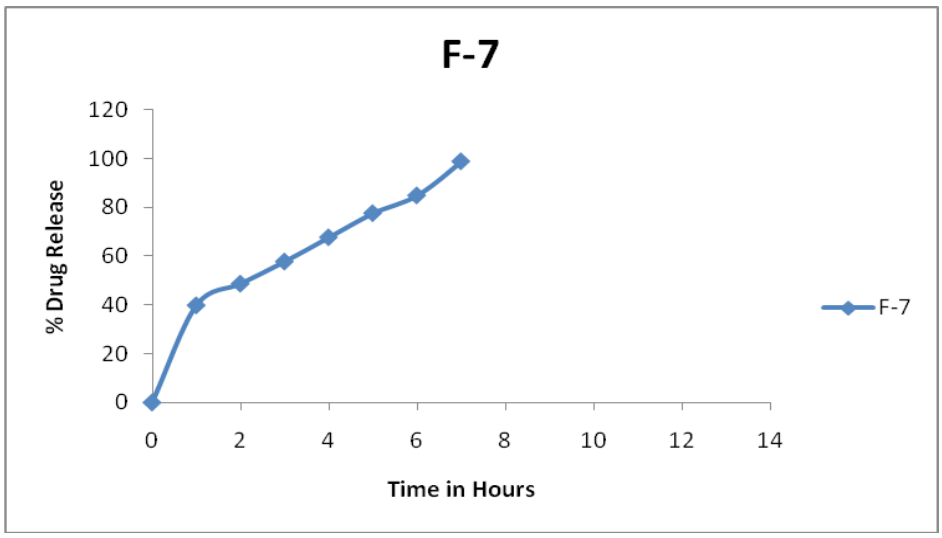


Fig. : Percent Drug Released Vs Time Plots of formulations F 7

Table no:24

TIME	FORMULATION -8
0	0
1 hrs	27.57%
2 hrs	35.65%
3 hrs	52.5%
4 hrs	65.45%
5 hrs	75.36%
6 hrs	81.94%
7 hrs	98.78%
8 hrs	-
9 hrs	-
10hrs	-
11hrs	-
12hrs	-

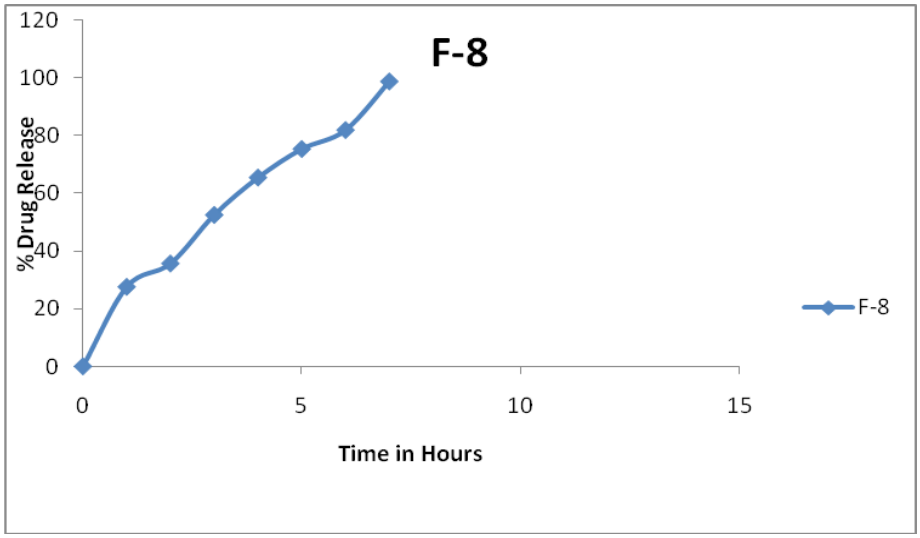


Fig. : Percent Drug Released Vs Time Plots of formulations F 8

Table no:25

TIME	FORMULATION -9
0	0
1 hrs	10.3%
2 hrs	16.38%
3 hrs	23.7%
4 hrs	30.48%
5 hrs	41.59%
6 hrs	48.7%
7 hrs	54.5%
8 hrs	68.05%
9 hrs	79.1%
10hrs	84.72%
11hrs	95.14%
12hrs	98.67%

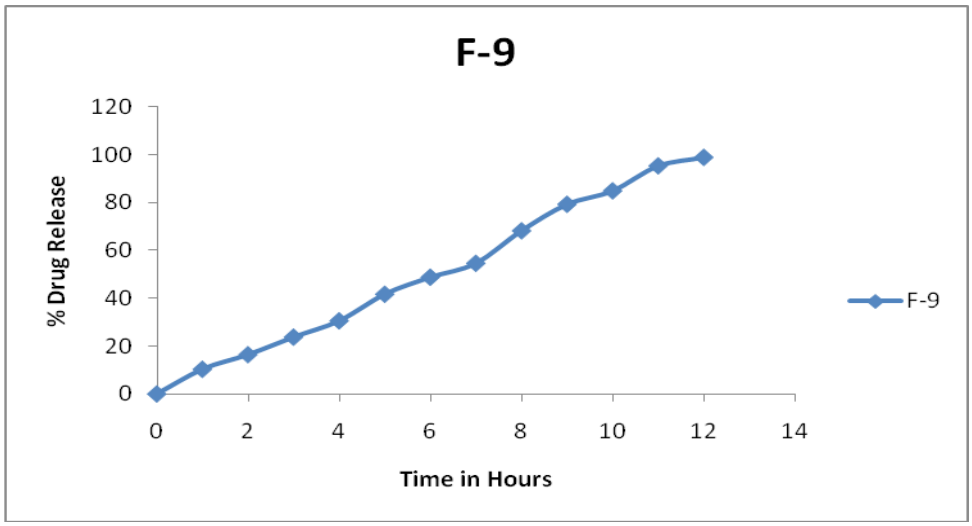


Fig. : Percent Drug Released Vs Time Plots of formulations F 9

Table no:26

TIME	FORMULATION -10
0	0
1 hrs	7.25%
2 hrs	11.55%
3 hrs	19.31%
4 hrs	25.85%
5 hrs	32.25%
6 hrs	43.38%
7 hrs	52.75%
8 hrs	64.67%
9 hrs	72.35%
10hrs	85.7%
11hrs	96.55%
12hrs	98.36%

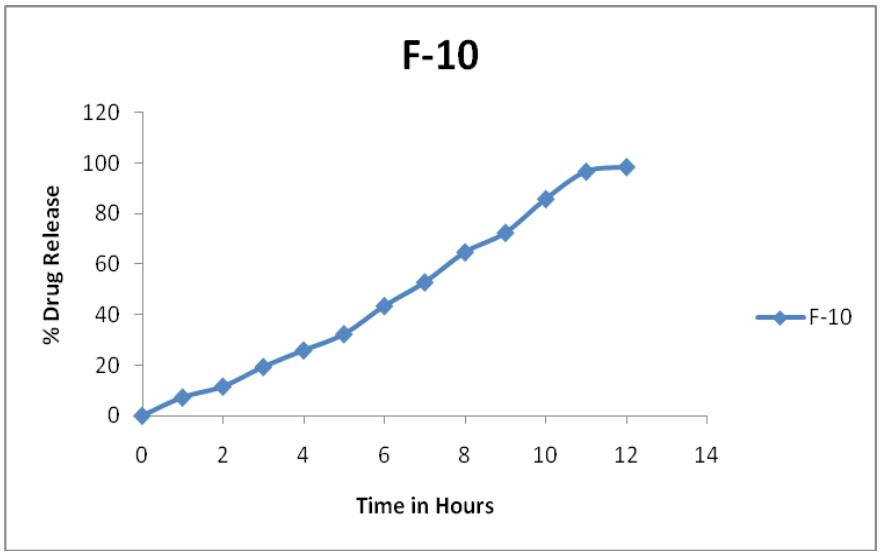


Fig. : Percent Drug Released Vs Time Plots of formulations F 10

Table no:27

TIME	FORMULATION -11
0	0
1 hrs	27.57%
2 hrs	41.24%
3 hrs	51.44%
4 hrs	61.2%
5 hrs	68.65%
6 hrs	77.25%
7 hrs	81.71%
8 hrs	85.95%
9 hrs	89.75%
10hrs	92.1%
11hrs	95.13%
12hrs	97.28%

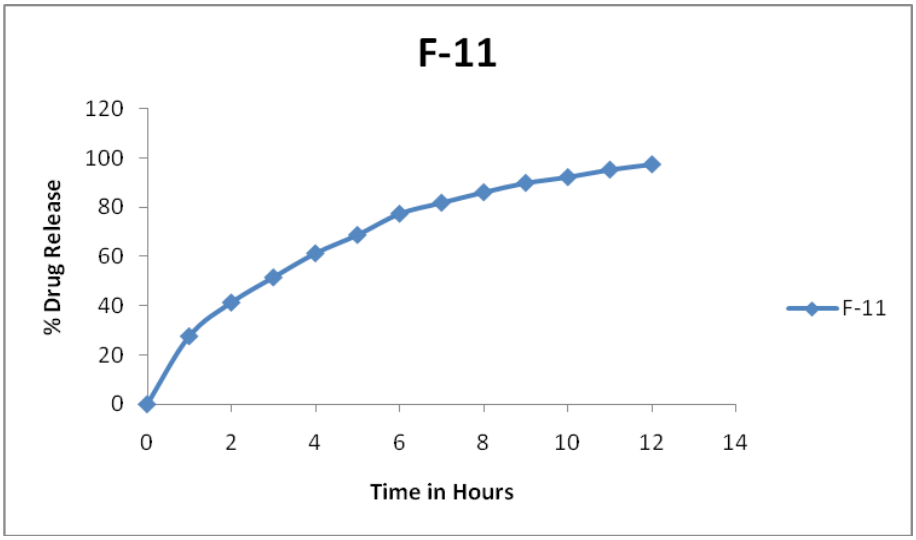


Fig. : Percent Drug Released Vs Time Plots of formulations F 11

Table no:28

TIME	FORMULATION -12
0	0
1 hrs	44.31%
2 hrs	59.82%
3 hrs	78.74%
4 hrs	84.5%
5 hrs	92.36%
6 hrs	99.74%
7 hrs	-
8 hrs	-
9 hrs	-
10hrs	-
11hrs	-
12hrs	-

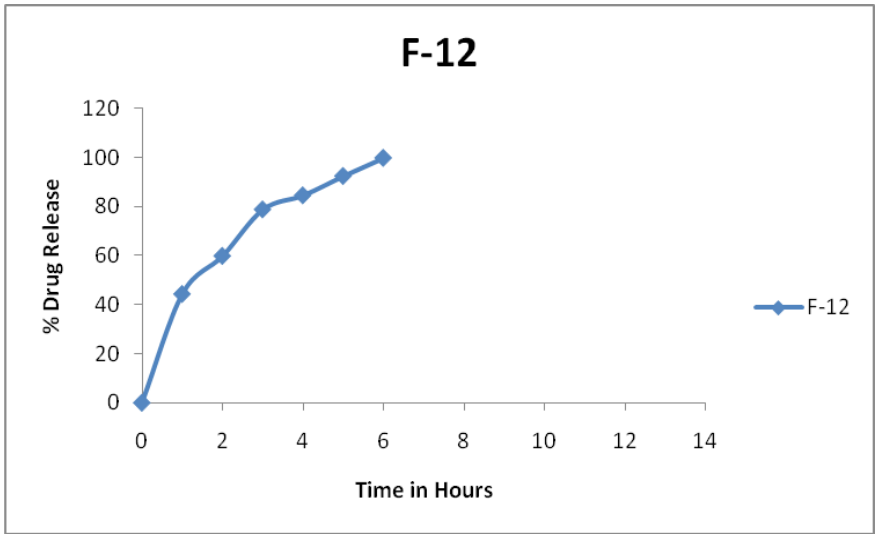


Fig. : Percent Drug Released Vs Time Plots of formulations F 12

Table no:29

Formulations	Parameters		
	T_{50}% (Mints)	T_{70}% (Mints)	T_{90}% (Mints)
F1	348	528	702
F2	408	576	0
F3	252	480	0
F4	432	606	0
F5	282	444	672
F6	312	498	678
F7	138	258	384
F8	174	276	396
F9	356	492	636
F10	414	528	624
F11	174	318	570
F12	90	156	282

The floating tablet of levetiracetam was designed to retend the drug for a time interval of minimum 12 hrs which will enhance the bioavailability as well as will extend the duration of action of the nootropic drug. Toward this approach the tablet was formulated using different polymers such as HPMC K4M, HPMC E15, Carbopol 974 P. Further the effect of gas forming agent $NaHCO_3$ on the buoyancy of the tablet

was also studied. The results indicated that the tablets from the batch F2 produced a maximum retardant effect and a buoyancy time which is higher than 24 hours. The formulation F12 produced a least retardant effect which was evident from the invitro drug release profile showing $t_{50\%,}$ $t_{70\%,}$ and $t_{90\%}$of 90 mins, 156 mins and 282 mins respectively. The buoyancy time also was found to be only 6 hrs for the batch F12. The formulation F2 produced the maximum retardant effect and buoyancy time was composed of Levetiracetam 500 mg, HPMC K4M 100mg, HPMC E15 150mg, and $NaHCO_3$ 100mg. while F3 composed of higher HPMC E15 and lower HPMC K4M quantities revealed a less retardant effect than F2 suggesting that the ability to retard the release of the drug mainly rely on the polymer HPMC K4M rather than HPMC E15 and also the buoyancy time was found to be lower than the formulation F3. The formulation F4 also revealed the aforementioned hypothesis, which was evident from its invitro data and buoyancy time. The formulation F4 showed a comparable higher invitro drug release resulting due to the decrease of quantity of sodium bicarbonate leading to decreased buoyancy time. This effect might have been caused by the less amount of CO_2 produced which in turn makes it less porous and higher denser and hence resulting in reduction of floating time which has initiated a higher drug release. The formulation F1 with a higher quantity of sodium carbonate invitro drug release also strengthens the aforementioned conclusion. The formulation F5 incorporated with lactose also decreased the $t_{50\%,}$ $t_{70\%,}$ and $t_{90\%}$ values and this can be attributed to the solubility of lactose in the dissolution medium and hence enhance the penetration of the dissolution medium resulting in faster release of the drug. The formulations F 11, F10, F9 and F8 were incorporated with the swellable water insoluble gel forming polymer Carbopol 974P. Carbopol 974 P forms water insoluble gel into which the drug is entrapped resulting in supersaturation of drug inside it. This results in

enhanced solubility and further leeching of the drug into the drug dissolution medium which is evident from the invitro drug release studies. Further when the drug levetiracetam is depleted from the tablet it results in the formation of pores ending up in the increased erosion of the tablet. This is evident from the buoyancy time of the formulations incorporated with carbopol.

SUMMARY

The objective of present study was to develop floating tablets of levetiracetam in order to achieve an extended retention in the stomach and thereby increase the bioavailability and study the release characteristics with twelve formulations.

The formulation was done by wet granulation method and the granules prepared were evaluated for the preformulation parameters such as bulk density, tapped density, angle of repose, carr's index and hausner ratio.

Tablets were prepared by wet granulation method. Tablets were evaluated for their physiochemical properties like angle of repose, hardness, friability, weight variation, thickness, compressibility studies, etc.

Tablets were then subjected to in-vitro release in pH 1.2 gastric stimulating the pH of stomach for about 12 hours using dissolution apparatus.The dissolution profiles for the formulation showed an initial burst release followed by controlled and sustained release.

CONCLUSION

From the above results obtained it can be concluded that the formulations possessing higher concentration of HPMC K4M possess good retardant effect of the drug levetiracetam and also increase the residence of the drug indicated by its increased buoyancy time. In particular batch F2, with HPMC K4M 100MG, HPMC E15 150 mg, sodium bicarbonate 100 mg and levetiracetam 500 mg has a good retardant and retention effect. The formulations incorporated with lactose, carbopol enhanced the leeching of the drug from the tablet gel matrix. However the batch F2 has fulfilled the objectives of our study and can be satisfactorily used for increasing patient compliance.

LEVETIRACETAM FLOATING TABLETS

Drug Excipient compatibility study:

Drug : Excipient	Ratio	Stability condition	Imp A (%)	Imp B (%)	Imp C (%)	Imp D (%)	Unknown Imp	Total Imp
API	-	INITIAL	ND	ND	ND	0.02	ND	**0.02**
		40°C/75%RH-1M	ND	ND	ND	0.02	ND	**0.02**
		40°C/75%RH-2M	ND	ND	0.01	0.03	0.01	**0.05**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.04**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.02**
API + HPMC K4M	1 : 1	INITIAL	ND	ND	0.01	0.02	ND	**0.03**
		40°C/75%RH-1M	ND	ND	0.01	0.02	ND	**0.03**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-3M	ND	ND	0.01	0.02	0.02	**0.05**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.02**
API + HPMC E 15	1 : 1	INITIAL	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-1M	ND	ND	ND	0.02	ND	**0.02**
		40°C/75%RH-2M	0.01	ND	0.01	0.03	ND	**0.05**
		40°C/75%RH-3M	ND	ND	0.01	0.02	0.02	**0.05**
		50°C/90%RH-1M	0.01	ND	ND	0.02	ND	**0.03**
API + Carbopol 974 p	1 : 1	INITIAL	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-1M	ND	ND	0.01	0.02	0.01	**0.04**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.04**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.02**
		INITIAL	ND	ND	ND	0.02	ND	**0.02**

API + sodium bicarbonate	1 : 1	40°C/75%RH-1M	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.04**
		50°C/90%RH-1M	ND	ND	0.01	0.03	ND	**0.04**
API + Lactose	1 : 1	INITIAL	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-1M	ND	ND	0.01	0.02	0.01	**0.04**
		40°C/75%RH-2M	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.04**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.02**
API + PVPK30	1 : 1	INITIAL	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-1M	ND	ND	ND	0.02	0.01	**0.03**
		40°C/75%RH-2M	ND	ND	ND	0.02	0.01	**0.03**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.04**
		50°C/90%RH-1M	ND	ND	ND	0.02	ND	**0.02**
API + Talc	-	INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-3M	ND	ND	ND	0.01	ND	**0.01**
		50°C/90%RH-1M	ND	ND	ND	ND	ND	**0**
API + Magnesium stearate	-	INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	0.01	ND	ND	ND	ND	**0.01**
		40°C/75%RH-3M	ND	ND	ND	ND	ND	**0**
		50°C/90%RH-1M	ND	ND	ND	ND	ND	**0**
HPMC K 4M		INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	ND	ND	ND	ND	ND	**0**

		40°C/75%RH-3M	ND	ND	ND	ND	0.01	**0.01**
		50°C/90%RH-1M	ND	ND	ND	ND	ND	**0**
HPMC E15	-	INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-3M	ND	ND	ND	ND	ND	**0**
		50°C/90%RH-1M	ND	ND	ND	ND	ND	**0**
Carbopol974p	-	INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-3M	ND	ND	0.01	ND	ND	**0.01**
		50°C/90%RH-1M	ND	ND	ND	ND	ND	**0**
Sodiumbi carbonate	-	INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-3M	ND	ND	ND	0.01	ND	**0.01**
		50°C/90%RH-1M	ND	ND	ND	ND	ND	**0**
Lactose	-	INITIAL	ND	ND	0.01	0.02	ND	**0.03**
		40°C/75%RH-1M	ND	ND	ND	0.02	0.01	**0.03**
		40°C/75%RH-2M	0.01	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-3M	0.02	ND	0.01	0.02	0.03	**0.08**
		50°C/90%RH-1M	0.04	ND	ND	0.02	0.01	**0.03**
PVP	-	INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	ND	ND	ND	ND	ND	**0**

		40°C/75%RH-3M	ND	ND	ND	ND	0.01	**0.01**
		50°C/90%RH-1M	ND	ND	ND	ND	0.01	**0.01**
Talc	-	INITIAL	ND	ND	ND	0.02	ND	**0.02**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-3M	ND	ND	ND	ND	ND	**0**
		50°C/90%RH-1M	ND	ND	ND	ND	0.01	**0.01**
Magnesium stearate	-	INITIAL	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-1M	ND	ND	ND	ND	ND	**0**
		40°C/75%RH-2M	0.01	ND	ND	ND	0.01	**0.02**
		40°C/75%RH-3M	ND	ND	ND	ND	ND	**0**
		50°C/90%RH-1M	ND	ND	ND	ND	0.01	**0.01**
API+ HPMC K 4M + HPMC E 15 + Carbopol974p + PVPk30 + Sodium bi carbonate + Lactose + Talc + Magnesium stearate	1: 1: 1:1:1:1 :1:1:1	INITIAL	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-1M	ND	ND	ND	0.02	0.01	**0.03**
		40°C/75%RH-2M	ND	ND	0.01	0.02	0.01	**0.04**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.04**
		50°C/90%RH-1M	0.01	ND	ND	0.02	ND	**0.03**
HPMC K 4M + HPMC E 15 + Carbopol974p + PVPk30 + Sodium bi carbonate + Lactose + Talc + Magnesium stearate	1: 1: 1:1:1:1 :1	INITIAL	ND	ND	0.01	0.03	ND	**0.04**
		40°C/75%RH-1M	ND	ND	ND	0.02	0.01	**0.03**
		40°C/75%RH-2M	ND	ND	0.01	0.02	0.01	**0.04**
		40°C/75%RH-3M	ND	ND	0.01	0.03	ND	**0.04**
		50°C/90%RH-1M	0.01	ND	ND	0.02	ND	**0.03**

ND- Not detected

LIMIT: As per ICH Guideline Q3B (R2) impurities in new drug products, the limit for highest unknown impurity is NMT 0.2%

Conclusion:

Based on the above data it was concluded that, all the excipients which were taken for Drug: Excipients compatibility study were compatible with the drug substance. Based on the study results and innovator product composition the inactive excipients were selected for formulation of the product.

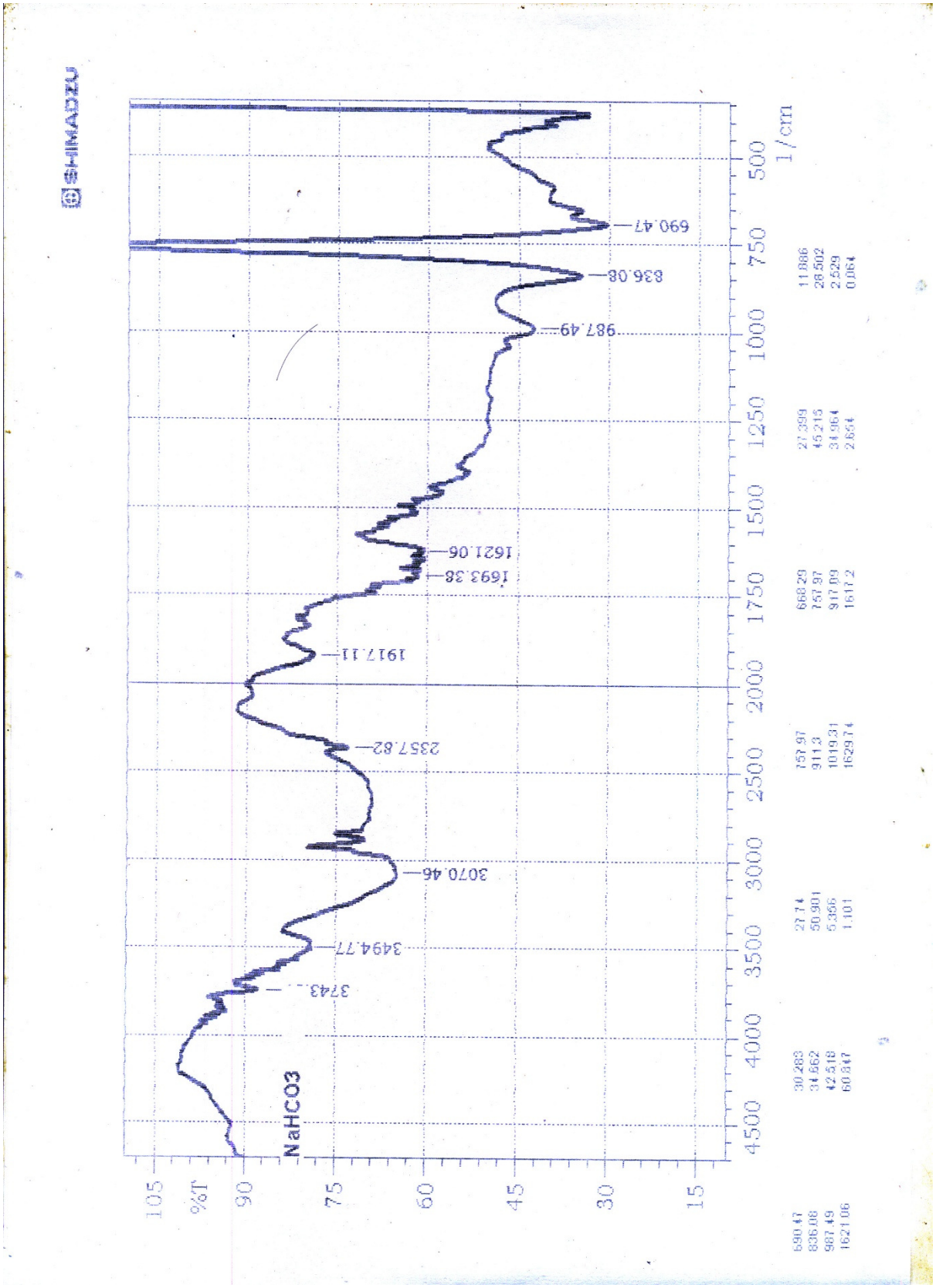


Figure 1 Sodiumbi Carbonate

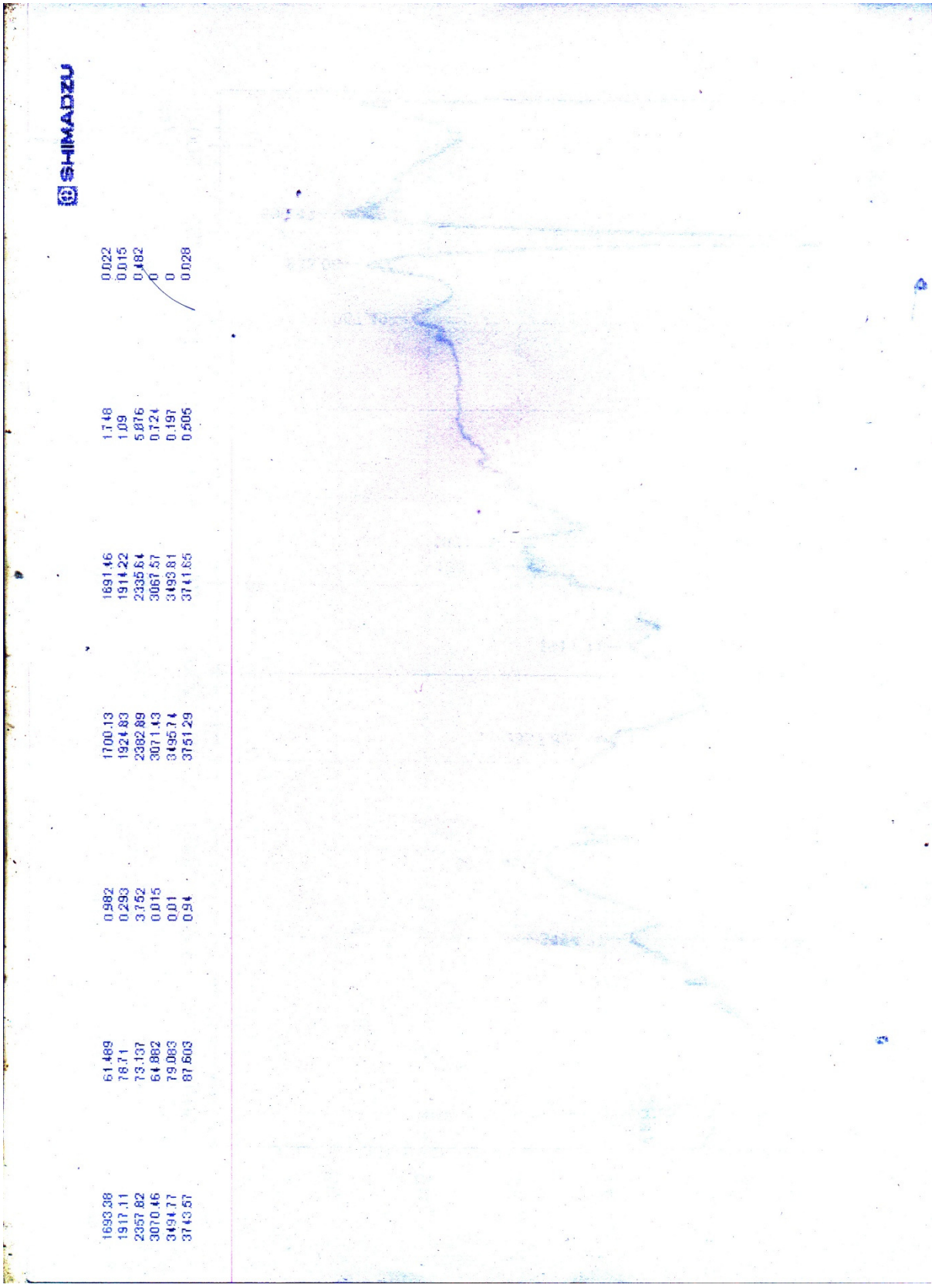


Figure 1(a) Sodiumbi Carbonate

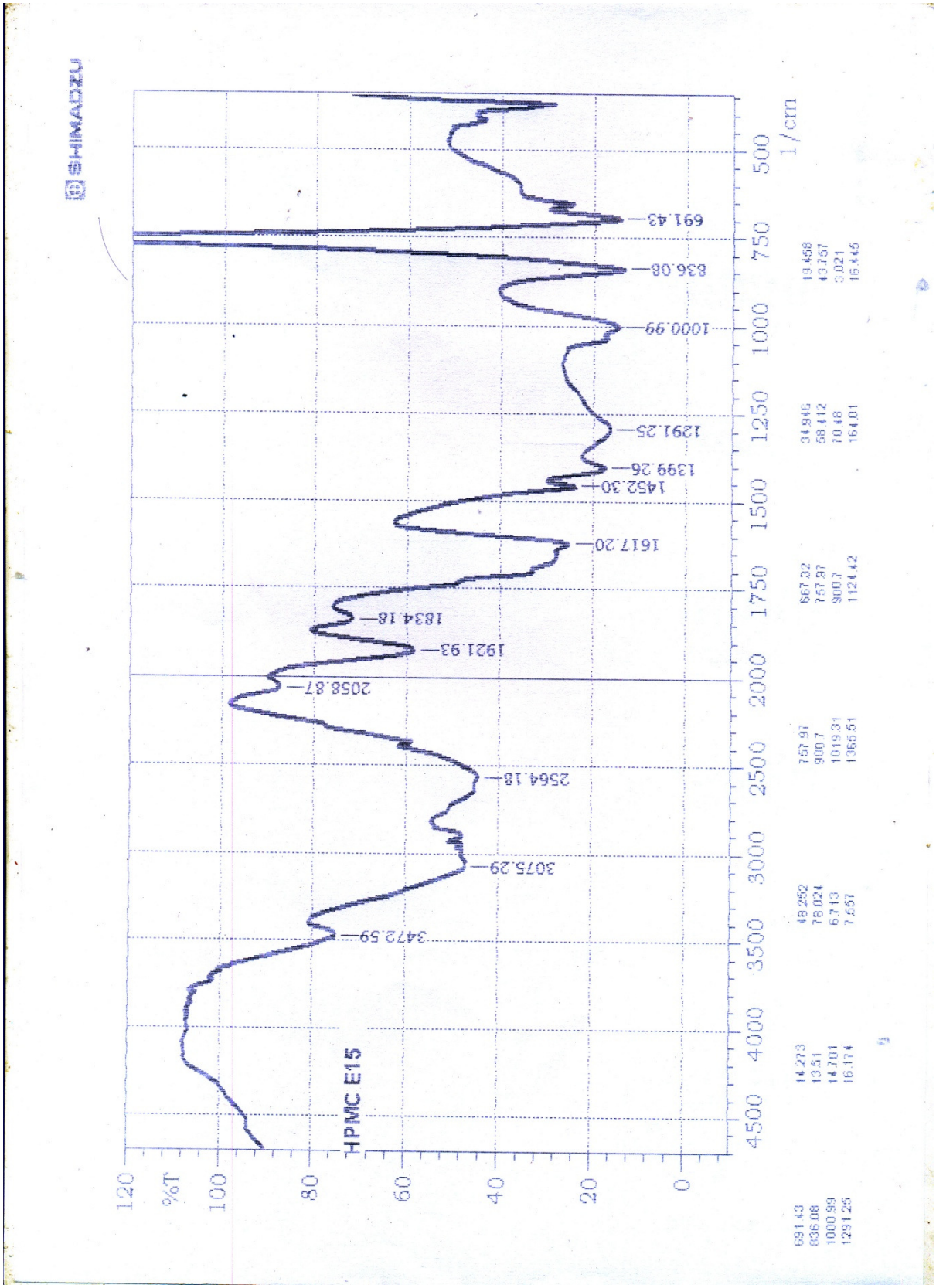


Figure 2 HPMCE15

Figure 2(a) HPMCE15

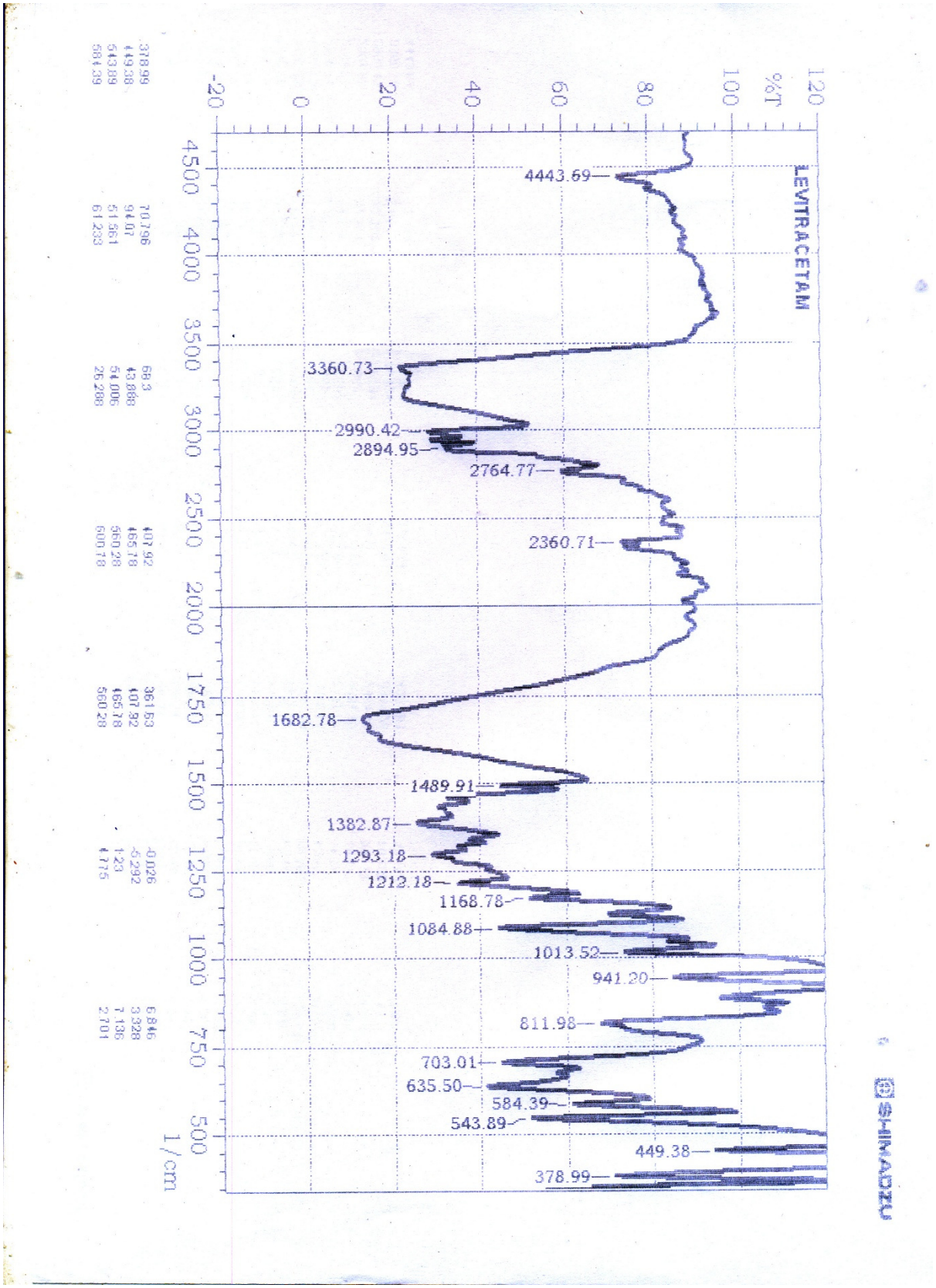


Figure 3 Levetiracetam

Figure 3(a) Levetiracetam

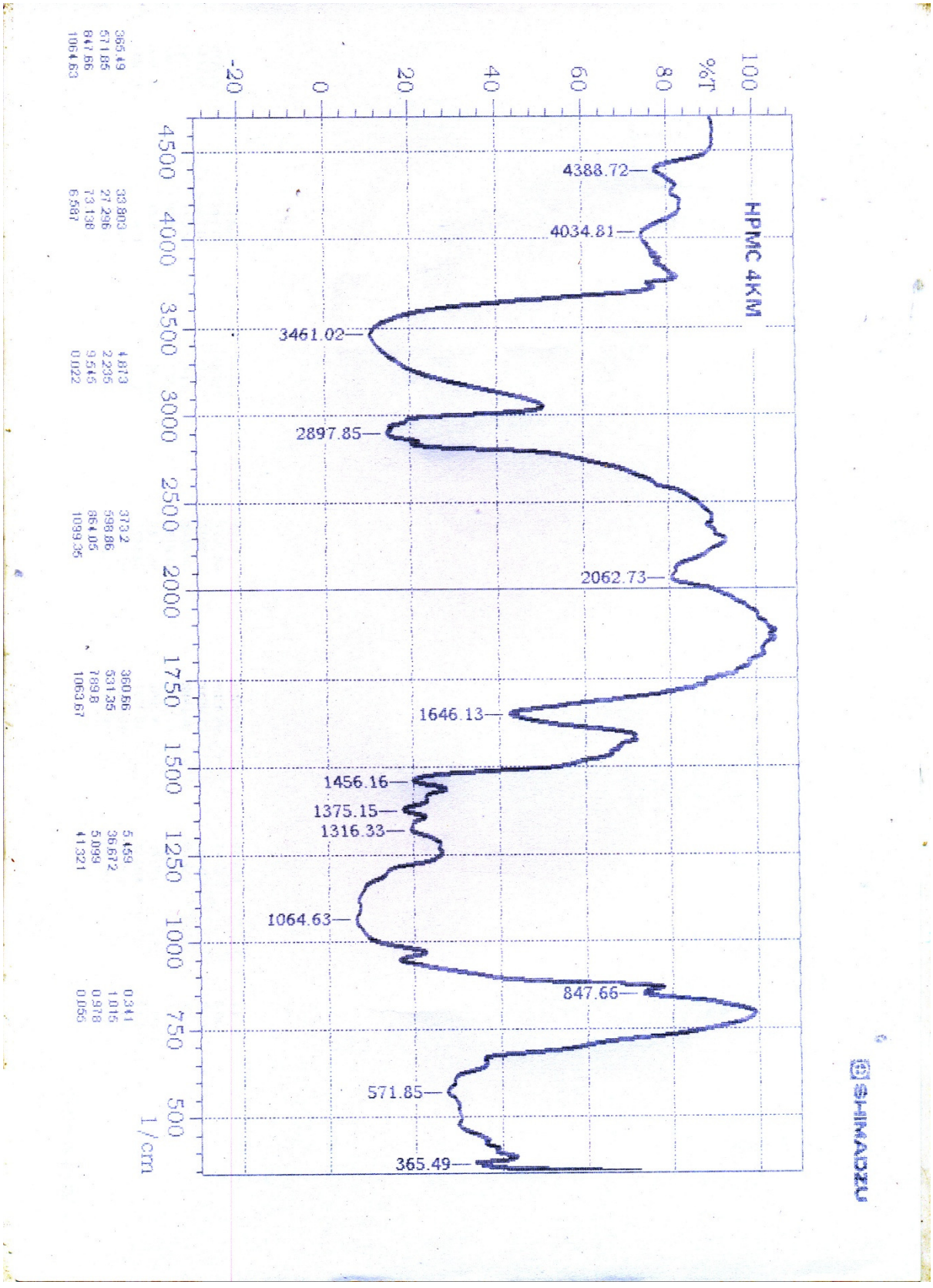


Figure 4 HPMCK4M

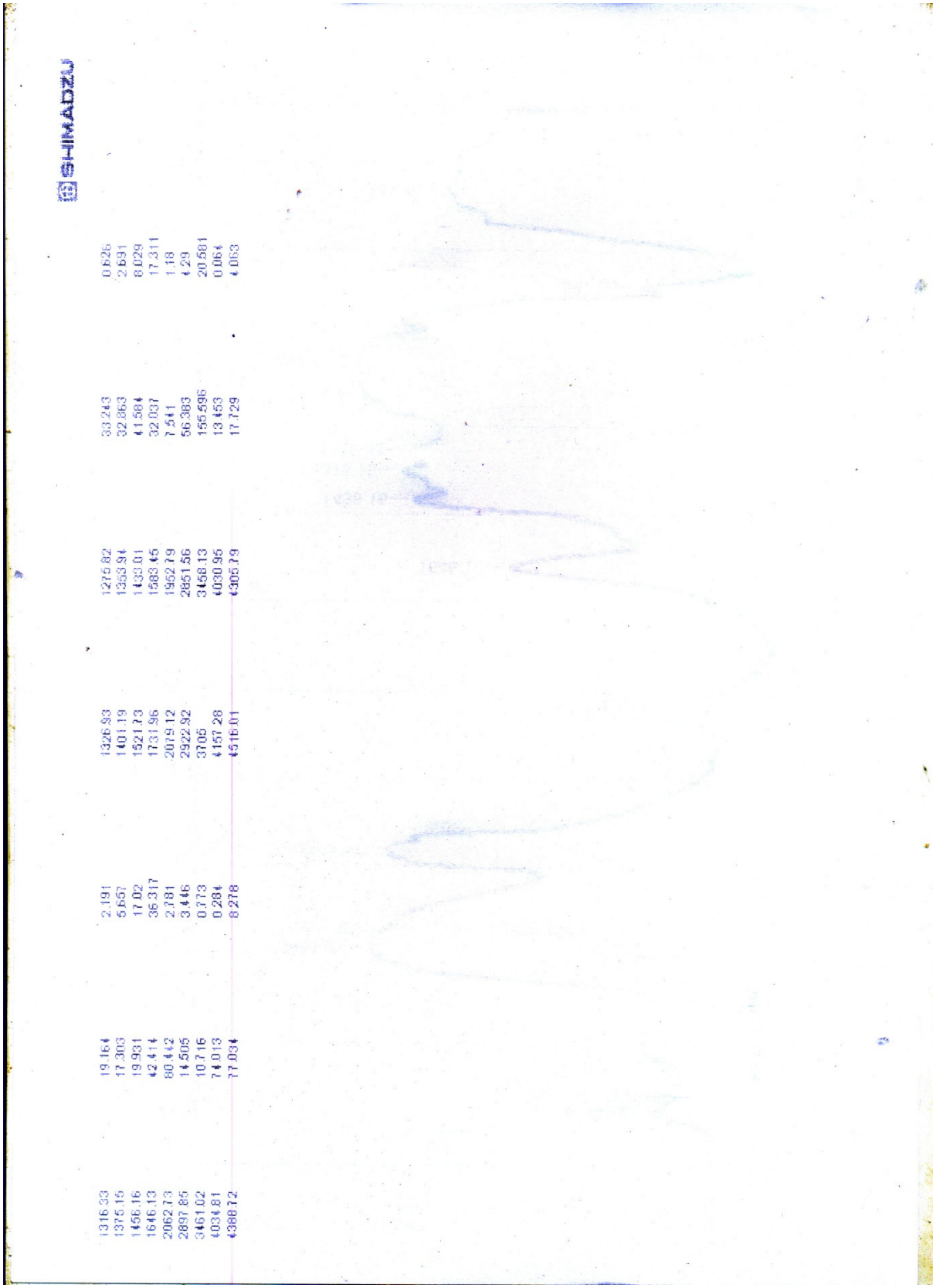


Figure 4(a) HPMCK4M

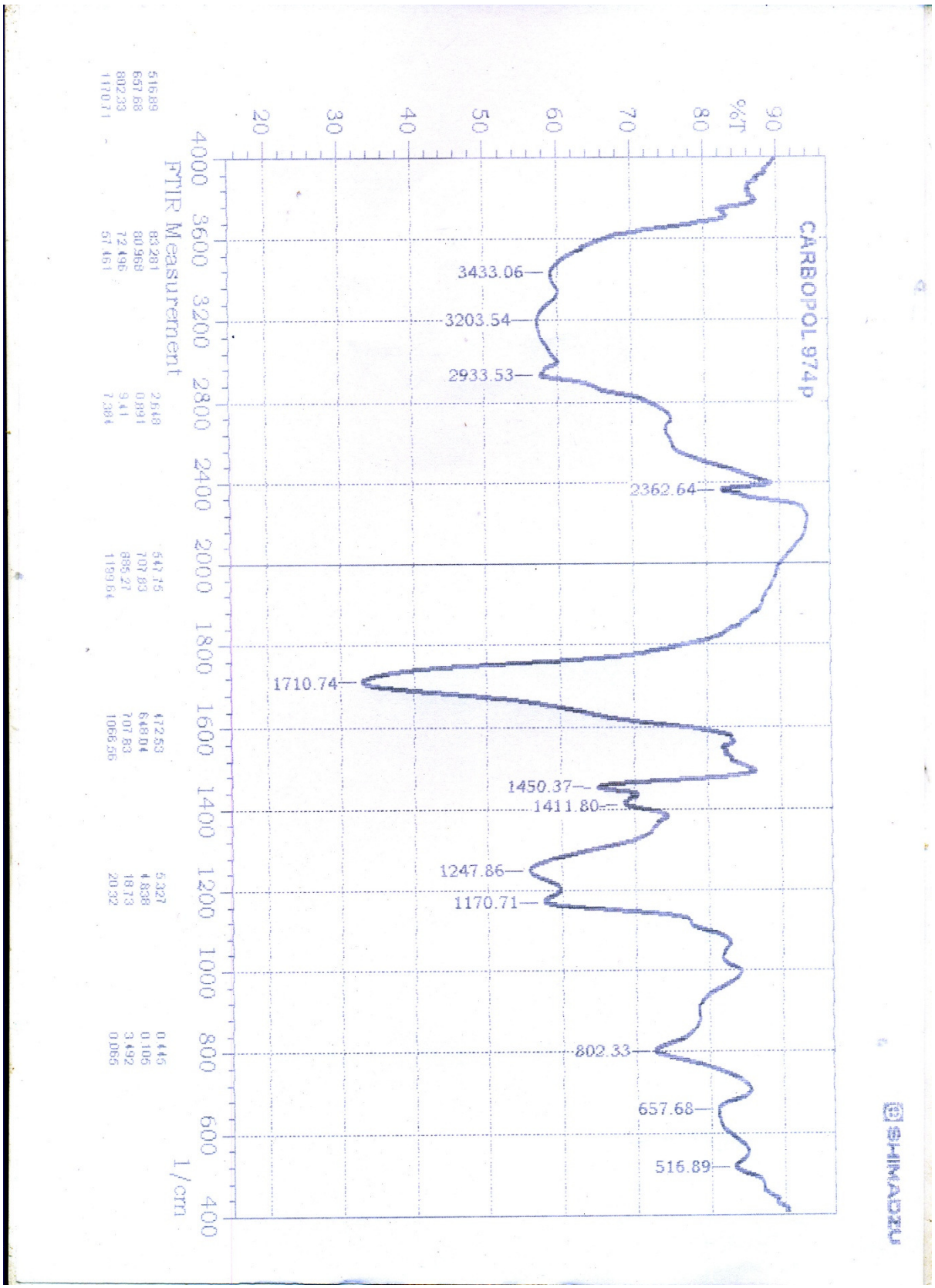


Figure 5 Carbopol 974P

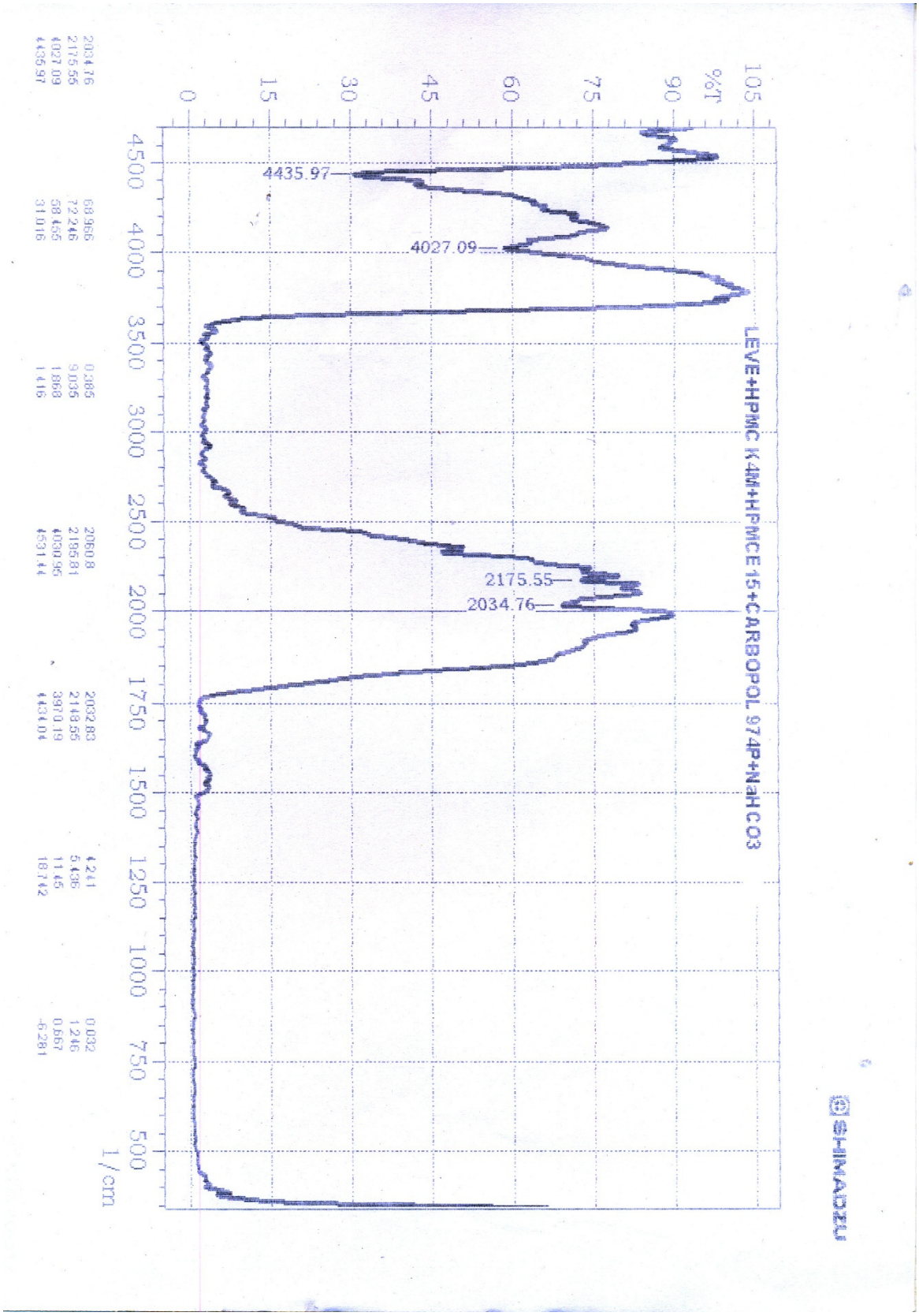


Figure 6 Levetiracetam + HPMCK4M + HPMCE15 + Carbopol 974P + Sodium bi carbonate

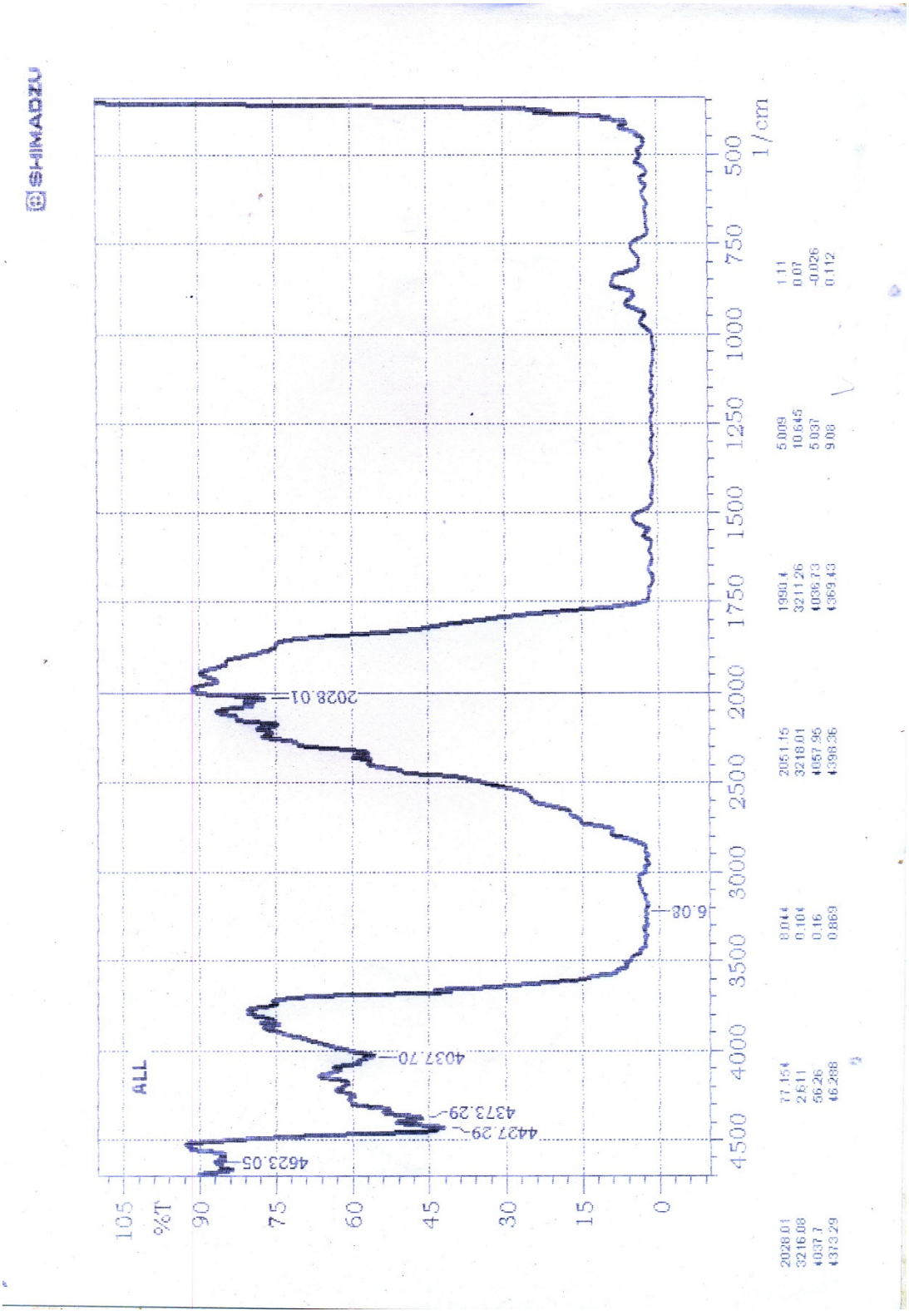


Figure 7 Levetiracetam + HPMCK4M + HPMCE15 + Carbopol 974P + Sodium bi carbonate + Talc + Magnesium Stearate

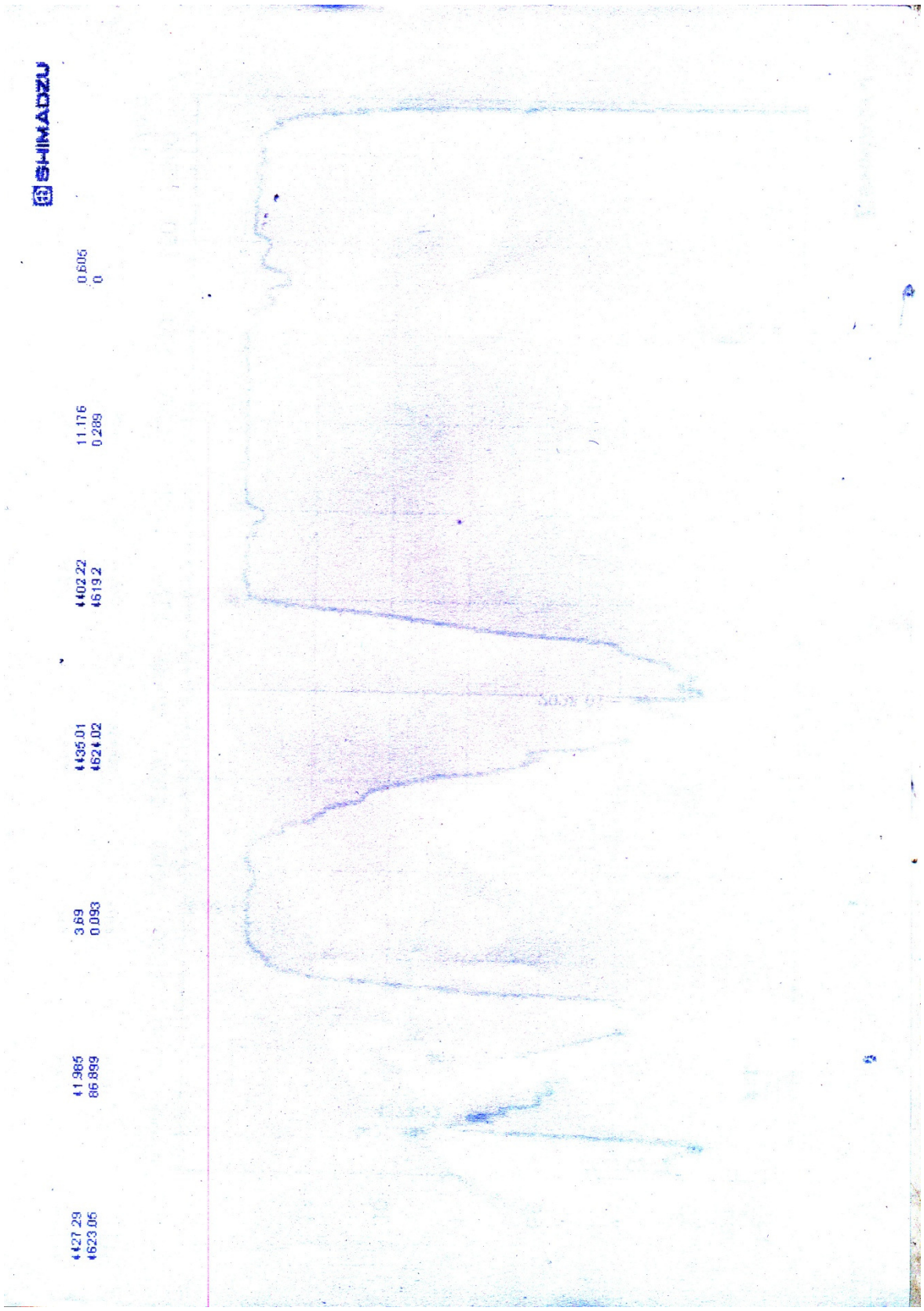


Figure 7(a) Figure 7 Levetiracetam + HPMCK4M + HPMCE15 + Carbopol 974P + Sodium bi carbonate + Talc + Magnesium Stearate

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